VOLUME 97 • FEBRUARY 1959 • NUMBER 2

DISEASES OF CHILDREN

Aldrich's Syndrome (Thrombocytopenia, Eczema, and Infection in Infants)
William Krivit and Robert A. Good

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Thomas H. Shepard, Benjamin H. Landing, and David G. Mason

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Kho Lien-Keng and O. Odang

Eye Injuries in Children
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Survival After Neuroblastoma with Widespread Metastasis
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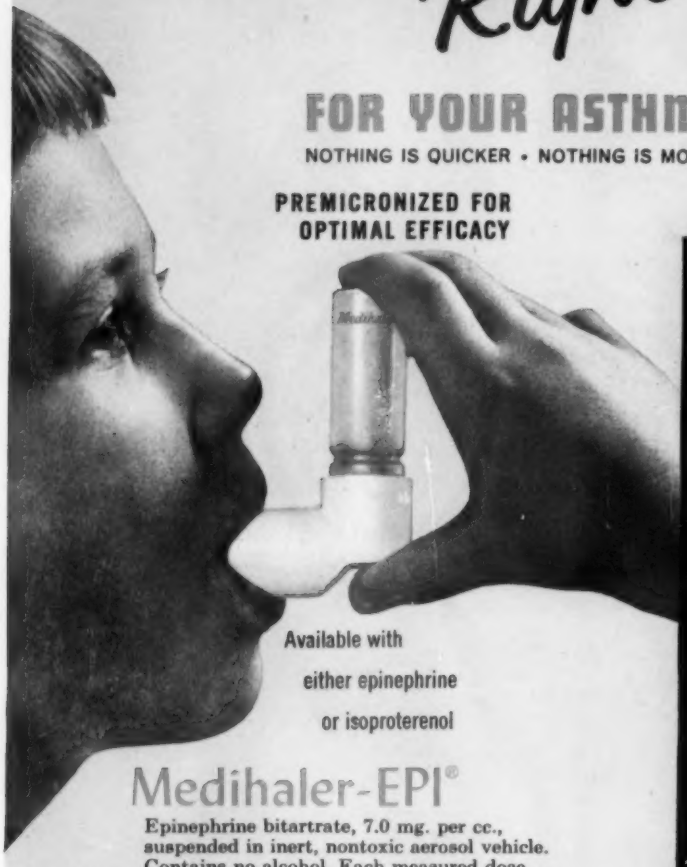

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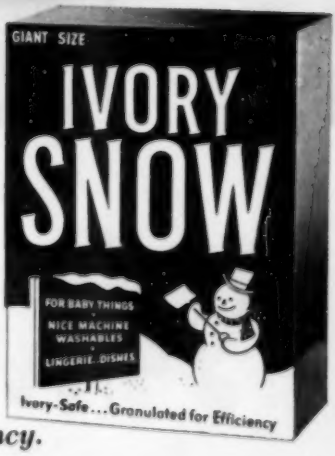

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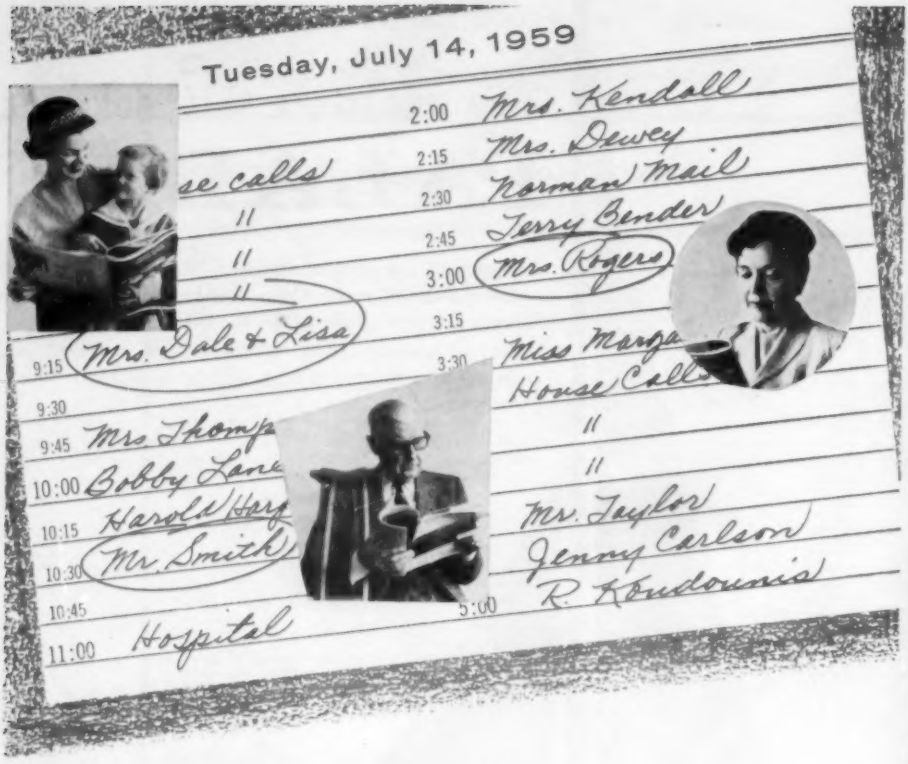

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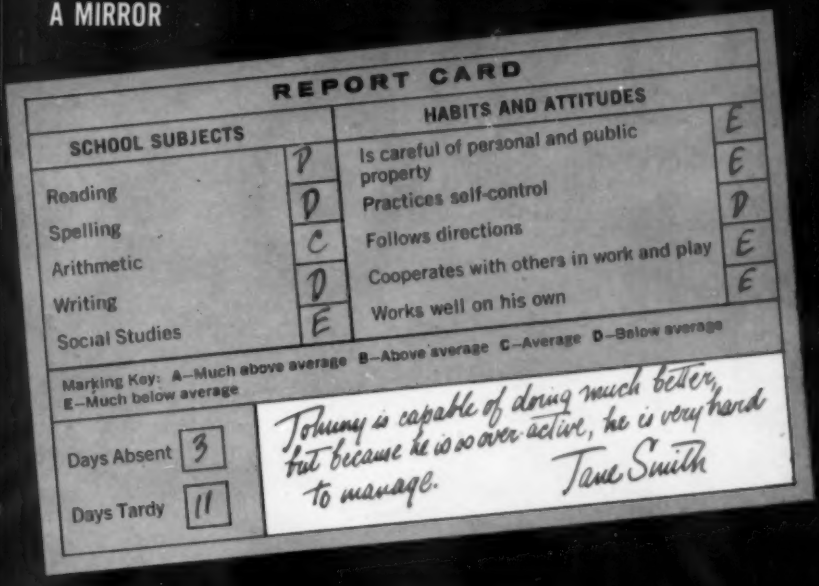
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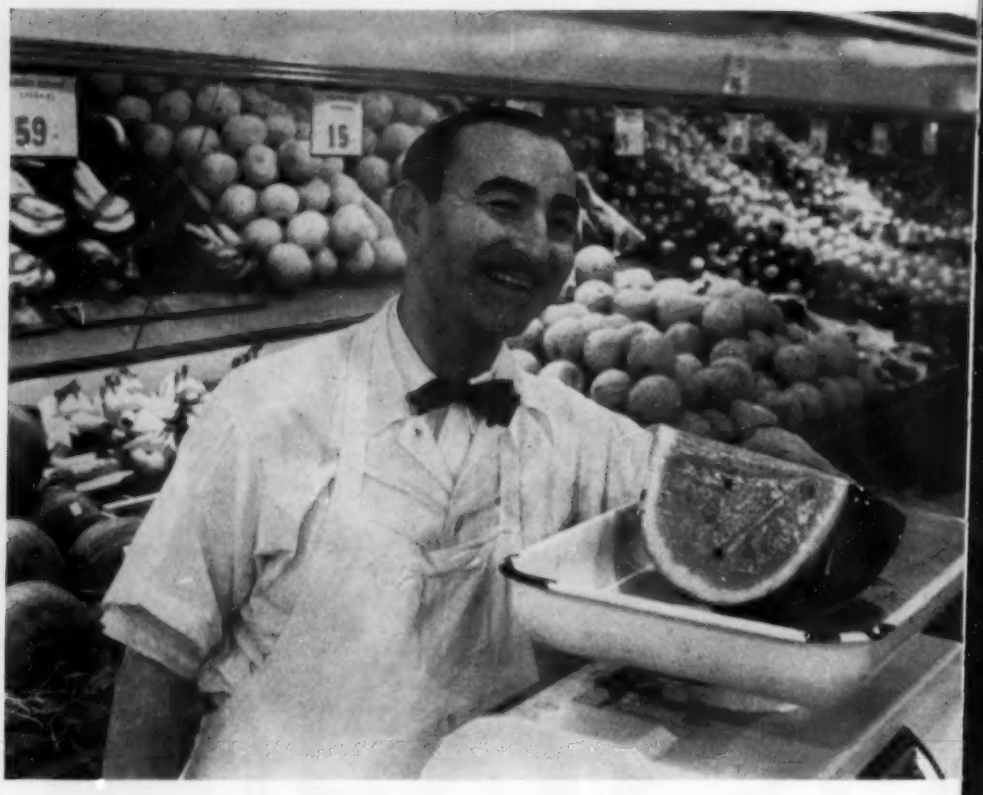

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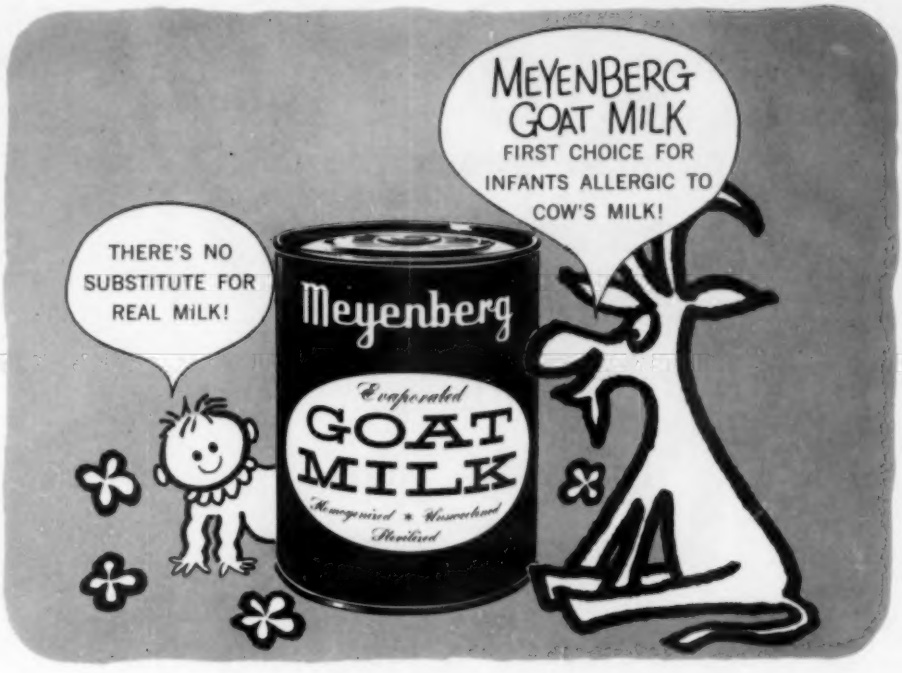

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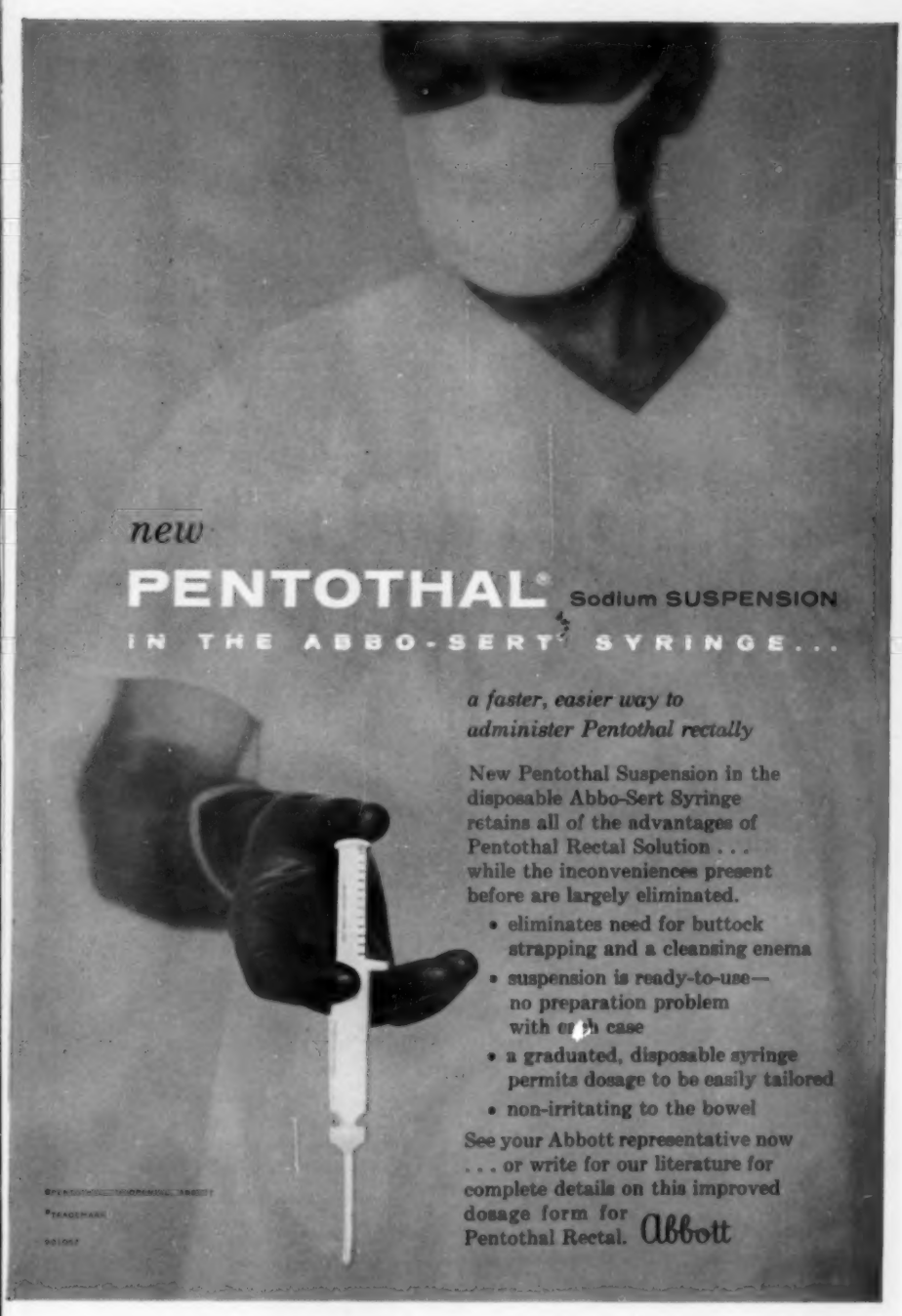
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1. Boland, E. W.: California Med. 89:417 (June) 1958. 2. Bunim, J. J., et al.: Arthritis & Rheumatism 1:313 (August) 1958. 3. Boland, E. W., and Hinsley, W. E.: Paper presented at the Annual Meeting, American Rheumatism Association, San Francisco, Cal., June 21, 1958. 4. Bunim, J. J., et al.: Paper presented at the Annual Meeting, American Rheumatism Association, San Francisco, Cal., June 21, 1958. 5. Sarre, T. G., et al.: South Med. J. 51:1060 (August) 1958.

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*Zinsser, H.: Bacteriology, ed. 11, New York, D. Appleton-Century Co., Inc. 1957, p. 244.

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DISEASES OF CHILDREN

Aldrich's Syndrome (Thrombocytopenia, Eczema, and Infection in Infants)

Studies of the Defense Mechanisms

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Aldrich, Steinberg, and Campbell,[1] in 1954, described a sex-linked recessive condition in infants which was characterized by draining ears, eczematoid dermatitis, and bloody diarrhea. Huntely and Dees,[2] and Wolff and Bertucio[3] reported 11 additional infants and children who have had the unusual triad of severe eczema, thrombocytopenia, and early death resulting from overwhelming infection. This disease appeared to be a definite entity which, although uncommon, is not extremely rare.

Because of the distressing morbidity and unfavorable prognosis despite all current therapy and because the etiology of this interesting syndrome remains an enigma, continued investigation of this disease was considered necessary.

It is the purpose of the present paper to report seven additional instances of this syndrome in which extensive morphological, immunological, hematological, endocrinological, and clinical investigations were completed.

Report of Cases

CASE 1.—This child was admitted to the University of Minnesota Hospitals at the age of 3 years, on June 25, 1952, because of bleeding and eczema. At 5½ months of age eczema and purpura were noted after a combined diphtheria and tetanus toxoids with pertussis vaccine injection. Severity of both eczema and purpura were variable, but neither completely disappeared. Three episodes of melena and one episode of severe epistaxis had required transfusions. Hematuria was also noted at 5 months of age. The patient had had frequent "colds and coughs" throughout his life, requiring antibiotic therapy on numerous occasions. Penicillin sensitivity was present. He had been breast fed for the first three months.

Physical Examination.—The weight was 12 kg. and the height 92 cm. The skin was covered with a dry eczematoid rash which was excoriated with blood crusts. Large ecchymotic areas and many petechiae over the lower extremities were noted. Tympanic membranes were diffusely inflamed. The gums bled easily. There were large palpable anterior and posterior cervical nodes. The liver was palpable 3 cm. below the costal margin, and the tip of the spleen was palpable.

Laboratory Examination.—The hemoglobin was 11.5 gm. %; the erythrocyte count was 4,500,000 per cubic millimeter, and the leukocyte count was 11,200 per cubic millimeter, with 88% neutrophils, 10% lymphocytes, and 2% monocytes. Platelets were 30,000 per cubic millimeter. Bleeding times were greater than 10 minutes. Cuff test was negative. Stool examination showed 3+ guaiac. Clotting time and prothrombin time were normal. Sedimentation rate was 20 mm. in one hour. Urinalysis was normal. Serum protein was 8.3 gm. %, with 3.9 gm. % albumin and 4.4 gm. % globulin. Calcium, phosphorus, and alkaline phosphatase were normal.

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Roentgenological survey did not reveal any abnormalities in the chest, long bones, or skull. Bone age was within normal limits.

Nose, throat, and blood cultures were negative.

Cell indices revealed mean corpuscular diameter (MCD) to be 7.5μ, mean corpuscular volume (MCV), 84 cu.μ, mean corpuscular hemoglobin (MCHb), 26μμg., and mean corpuscular hemoglobin concentration (MCHbC), 30%. Peripheral blood smears revealed a constant thrombocytopenia and eosinophilia.

Hospital Course.—Fever continued throughout his hospitalization despite antibiotic therapy. His platelet count remained at low levels. After intracerebral hemorrhage the patient died at another hospital.

Lymph Node Biopsy.—Sections showed minimal reticular hyperplasia, a few macrophages, and eosinophils. Normal architecture was present. No granuloma were noted.

Bone Marrow Aspiration.—The myeloid-erythroid layer was 10.6%. Neutrophils and precursors numbered 60.8%. Eosinophils were increased to 9.2%. Basophils numbered 0.4%; normoblasts, 13.8%, showed no abnormality; lymphoid cells, 15.8%, showed no alterations of significance. Plasma cells were present. Megakaryocytes were within normal limits. Platelet production was normal.

Case 2.—This 2-year-old white boy, brother of Case 1, was admitted to the University of Minnesota Hospitals on June 26, 1952, because of a history of purpura and infection.

The mother first noted a petechial rash on the abdomen at 3 days of life. Early eczematoid rash appeared on the face, arms, and legs. This did not seem to be aggravated by changes in formulae. Vomiting was noted for the first two months. Stools were loose and foul-smelling during this time, but no blood was noted. He weighed 10 lb. at the age of one year. He had had several severe infections, including pneumonia and cellulitis of eczematoid lesions.

Physical Examination.—This 22-month-old chronically ill-appearing child weighed 5.4 kg. and was 70 cm. in height. His occipital frontal circumference was 43.5 cm. Eczematoid lesions of the face and extremities were present. The tympanic membranes were bilaterally thickened and injected, and the landmarks were obscured. There was mucopurulent drainage from the nose. The pharynx and gums bled easily. Examination of the heart was negative. The liver and spleen were not palpable. Generalized lymphadenopathy was present.

Laboratory Examination.—Hemoglobin was 6.2 gm. %, and hematocrit was 20%. The cell indices were MCD, 8.0μ; MCV, 93 cu.μ; MCHb, 22μμg., and MCHbC, 32%. The white cell count was 20,000 per cubic millimeter with 79% neutrophils, 9% lymphocytes, 1% monocytes, 10% eosinophils, and 1% basophils. Platelets were 168,000 per cubic millimeter on only one count. Bleeding time was six minutes. Sedimentation rate was 7 mm. in one hour. Clotting time was normal. Prothrombin time was 18 minutes and control 12.6 minutes. Albumin was 2.5 gm. %, and globulin was 4.5 gm. %. Calcium, phosphorus, and alkaline phosphatase were normal. Reticulocytes were normal.

Bone Marrow Aspiration.—Bone marrow aspiration revealed eosinophila (6.4%), plasmacytosis (1.4%), normoblasts (27.8%), neutrophils and precursors (57.8%), and lymphoid cells (6.6%). Megakaryocytes were present, and there was evidence of platelet formation.

Roentgenological survey revealed normal skull and long bones. There was retardation of the bone age. Chest roentgenogram demonstrated an atelectasis of the right upper lobe.

Hospital Course.—He was given an elimination diet of Nutramigen (hypoallergenic formula), mashed bananas, carrots, rice cereal, and puréed lamb.

After discharge his clinical signs and symptoms continued without significant change. He continued to have purpura and recurrent infections. In November, 1952, he died at another hospital following an episode of "congestive heart failure and anemia." No autopsy was performed.

Case 3.—A 3-month-old white boy was admitted on July 20, 1953, because of blood in stools. Late on the first day of life the child passed a large amount of bright red blood per rectum, which had continued intermittently. Fever, chronic cough, and conjunctivitis were noted throughout the first three months. These symptoms persisted despite treatment with penicillin and sulfadiazine.

Physical Examination.—This 3-month-old chronically ill-appearing infant weighed 5.3 kg. and was 61 cm. in height. There was a conjunctivitis with a mucopurulent discharge. A 2×2 cm. swelling at the angle of the right jaw was observed which did not appear to be fixed to the mandible. The tip of the spleen was palpable. There was an eczematoid rash involving scalp and face and extending over the entire body.

Laboratory Examination.—Hemoglobin was 7.4 gm. %. The white cell count was 9,750 per cubic millimeter, with a differential of 53% neutrophils, 28% lymphocytes, 14% monocytes, 3% eosinophils, and 2% basophils. Platelet count was 28,000 per cubic millimeter. Cuff test was positive. Stools were always positive for occult blood. Mantoux test was negative.

Roentgenological survey revealed a swelling of soft tissue of the area adjacent to but not involving the left mandible. Examinations of the skull, long bones, upper gastrointestinal tract, and colon were normal.

Hospital Course.—Therapy of eczema consisted of symptomatic treatment. The soft tissue swelling disappeared. The bloody stools persisted despite treatment with a nonmilk formula. The eczema, although variable in intensity, persisted despite therapy.

At 7 months of age he was readmitted to the hospital because of a marked exacerbation of the dermatitis. Bilateral draining purulent otitis media was noted, and culture revealed Pseudomonas aeruginosa and Proteus species. The liver was palpable 4 cm. below the right costal margin. Thrombocytopenia and eosinophilia of the peripheral blood continued.

After second discharge from the hospital, the eczema improved and the melena disappeared for a period of one month.

However, on Dec. 8, 1953, he became lethargic and began to vomit. Upon readmission to the hospital, he was pale and had numerous petechiae over the entire body. The fontanelle was tight but not bulging. Slight opisthotonus was present. The liver was palpable 6 cm. below the right costal margin, and the spleen was palpable. No abnormal reflexes were present. Meningitis was suspected, and a lumbar puncture was performed. During this procedure the patient died. Postmortem cultures of blood, cerebrospinal fluid, and pericardial fluid were sterile.

Bone Marrow Aspiration.—Bone marrow aspiration revealed the following findings: normoblasts 33.2%, neutrophils and precursors 36.6%, myeloblasts 1.4%, eosinophils 5.0%, lymphoid cells 23.4%, and plasma cells 0.4%. Megakaryocytes were approximately normal in number and morphological appearance.

Skin Biopsy.—Biopsy of the skin revealed only a very mild nonspecific inflammatory change.

Autopsy.—The weight of the liver was 360 gm., and it extended 7 cm. below the right costal margin. The spleen weighed 25 gm. Petechiae were noted over the skin, heart, lungs, and kidneys. Considerable generalized lymphadenopathy was present.

Microscopic Section: The lung showed an increase in the number of cells in the alveolar walls. The cells were lymphocytes and polymorphonuclear cells. Some hemorrhage was present. The liver showed moderate infiltration of the periportal cells, with lymphocytes and hypertrophy of the reticuloendothelial cells. Lymph nodes demonstrated benign hyperplasia. The spleen showed diffuse proliferation of the reticuloendothelial cells, as well as considerable hemorrhage and sinusoidal congestion. Thrombosis of small vessels was noted in the heart, spleen, lymph nodes, kidneys, adrenals, and pancreas. These vascular lesions were interpreted as being similar to those observed in thrombotic thrombocytopenic purpura.

CASE 4.—This 8-month-old white boy was admitted to the University of Minnesota Hospitals on March 11, 1954, as a problem of purpura.

Bleeding was noted to be extensive following circumcision at 4 days of age. After any slight trauma he bruised. Eczema and purpuric rash were noted over the abdomen and face at 3 weeks of age. This had been intermittently present until admission. He had had frequent colds, which were treated with oral penicillin, and had a persistent and moderately severe cough. Three weeks prior to admission blood was noted in the stools.

Physical Examination.—This 8-month-old white boy was well developed and weighed 10 kg. There were small bruises noted on abdomen and back. Numerous petechiae were present over the entire body. Liver and spleen were not palpable. A rash compatible with the diagnosis of atopic eczema was present.

Laboratory Examination.—Hemoglobin was 12.9 gm. %; the white cell count was 6,850 per cubic millimeter, with a differential of 49% neutrophils, 40% lymphocytes, 6% monocytes, 4% eosinophils, and 1% basophils. Platelets were 34,000 per cubic millimeter. Bleeding time was 14 minutes. Sedimentation rate was 12 mm. in one hour. Rumpel-Leede test was positive. Mantoux skin test was negative.

Hospital Course.—Corticotropin (ACTH), 12.5 mg. q. 6 h., was started on March 19 and continued until April 6. On this regimen his platelet count increased to 130,000, on March 24, but subsequently fell to 68,000, on April 4. The bleeding time on March 24 was 12 minutes. Cortisone was then substituted in dosages of 12.5 mg. q. 6 h. and was continued on an outpatient basis. Before discharge on April 10 his platelet count was 67,000 per cubic millimeter.

The eczema and purpura disappeared on the steroid therapy. He was readmitted two weeks later, at which time his platelet count was 25,000 and his bleeding time was over 15 minutes. The cortisone was discontinued on April 29. He had a cough and coryza, and x-ray of the chest revealed a pneumonia of the left upper lobe. He was treated with tetracycline.

An unexplained episode of syncope was noted on May 20 following a minimal upper respiratory infection. This episode of sudden collapse was attributed to a postcortisone adrenal unresponsive state. He recovered well and uneventfully in several hours.

On June 16 the patient was readmitted because of recurrence of bruising. On this admission, right otitis media and pharyngitis were noted. Antibiotic therapy was instituted. On June 25 a splenectomy was done. The platelet response was gratifying in that he maintained levels between 122,000 and 242,000 postoperatively. Cortisone was given at

time of splenectomy and continued until June 30. There was a slight wound infection noted on July 16 which healed spontaneously.

On Aug. 7, without any prodromal symptoms or signs, the patient had a sudden temperature elevation to 107 F. He died 6 hours later. Profound shock was noted during the preceding several hours, and numerous petechiae were present around the mouth.

Bone Marrow Aspiration.—Bone marrow aspiration at the time of the initial admission demonstrated an increase in the megakaryocytes. There was some evidence of the morphological change in the megakaryocytes referred to by Dameshek as megakaryocytic arrest.

Autopsy.—Weight of the spleen was 35 gm. The follicles had a normal appearance. There was no congestion of sinusoids.

Gross examination at the time of the autopsy revealed bilateral adrenal hemorrhage.

CASE 5.—This patient was admitted to the University of Minnesota Hospitals on July 19, 1955, at 16 months of age, because of recurrent infections, otitis media, bloody diarrhea, and bleeding.

At 11 days of age he had developed bloody stools and diarrhea, for which he was hospitalized three weeks. At 2 months of age he had had moderately severe atopic eczema. Recurrent and severe episodes of bloody diarrhea and fever were noted which necessitated frequent hospitalizations. Treatment of eczema consisted of topical cortisone, dietary restrictions, and coal tar preparations. He was given multiple transfusions.

At 8 months of age he had had a "crisis," with recurrence of diarrhea and severe dehydration which responded to parenteral fluids. At 9 months bilateral purulent drainage of both ears was noted from which Pseudomonas was cultured. The eczema showed variability without relationship to therapy.

Because of recurrent fever he was treated with chloramphenicol at 11 months of age. Following this, agranulocytosis was first noted (1,500 white cells per cubic millimeter with 90% lymphocytes). Therapy consisted of transfusion, after which his white cell count rose to normal level. Further illnesses included recurrent otitis media and pneumonia despite prophylactic oxytetracycline (Terramycin). Because of the persistence of eczema, loose stools, and furunculosis, he was referred to the University of Minnesota Hospitals.

Physical Examination.—This 14-month-old chronically ill infant weighed 10 kg. and was 78 cm. in height. There was a severe dermatitis of the scalp and erythematous bleeding areas over the entire body. Conjunctivitis and blepharitis were present in the left eye. Chronic otitis media was present. The liver and spleen were not palpable.

Laboratory Examination.—The hemoglobin was 10.6 gm. %, the white cell count was 8,200 per cubic millimeter, with a differential of 32% neutrophils, 59% lymphocytes, 6%, monocytes, and 3% eosinophils. Platelet count was 24,000 per cubic millimeter. Positive benzidine and guaiac tests for occult blood in the stools were noted. On Aug. 9 the white cell count fell to 1,500 per cubic millimeter and the neutrophils decreased to 16%. Following massive transfusions and antibiotic therapy the white cell count rose to 2,600, with 26% neutrophils.

Hospital Course.—He received symptomatic therapy to the skin. Skin and lymph node biopsy were done on Aug. 3, and after these he developed an abscess at site of biopsy. Large "hemorrhagic plaques" were noted over the scalp, and following an episode of pneumonia and paralytic ileus the patient died, on Aug. 15, despite transfusions and antibiotic therapy.

Bone Marrow Aspiration.—Marrow was hyperplastic. Normoblasts were 24.2%. Neutrophils were normal (39.0%). Basophils (0.2%) and eosinophils (2.4%) were normal. Lymphoid series (34.2%) contained normal numbers of plasma cells. Megakaryocytes were normal in number.

Lymph Node Biopsy.—Moderate reticular hyperplasia was noted and was considered as benign hyperplasia.

Skin Biopsy.—There were a few scattered lymphocytes in the dermis which were considered as evidence of mild chronic inflammation of the skin. No large reticulum cells like those observed in Letterer-Siwe's disease were present.

Autopsy.—Gross Examination: The skin showed numerous red ulcerated well-demarcated circular lesions over the occipital and cervical areas. An abscess containing 10 cc. of purulent material was noted in the left thigh. The weight of the liver was 700 gm.; it extended 7 cm. below the right costal margin and appeared pale and soft. The weight of the spleen was 90 gm. Fibrin adhesions were noted over the entire spleen. Lymph follicles were very distinct. Petechiae were noted on the surface of the heart, lungs, and kidneys.

Microscopic Examination: In the lungs extensive intra- pulmonary hemorrhage and pneumonitis were present. In the gastrointestinal tract an ulceration of the large bowel extending to the muscular layer was found and superficial ulceration of the stomach was present. The liver showed mild central lobular congestion. A section of one of the scalp lesions revealed ulceration, hemorrhage, and extension of a leukocytic (mononuclear and polymorphonuclear) infiltration throughout the ulcer bed and down the fibrous septae into subcutaneous fat and deep fibrous layers.

CASE 6 (Figs. 1-3).—This 11-month-old white boy was admitted to the University of Minnesota

Fig. 1 (Case 6).—Age 11 months. Characteristic distribution of eczema over face, arms, and legs with sparing of abdominal area.

Hospitals on Sept. 11, 1956, with a diagnosis of eczema and purpura.

Bleeding per rectum was noted on the sixth day of life. At 3 months of age eczema of the face was noted which gradually spread to most areas of the body. Therapy consisting of Mull-Soy (hypoallergenic soy food), Nutramigen, and hydrocarbons did not alleviate the eczema. At 6 months he weighed 14 lb. Because of rectal ulcer bleeding he became anemic and received blood transfusions. Anorexia, vomiting, and dark tarry stools were present for five days prior to admission.

Physical Examination.—This 11-month-old chronically ill boy was 70 cm. long and weighed 6,380 gm. The infant appeared to be malnourished. Generalized eczema was present over the entire body. Generalized lymphadenopathy was present. The liver was palpable 3 cm. below the costal margin. The spleen was not palpable.

Laboratory Examination.—Hemoglobin was 10.9 gm. %; erythrocytes, 3,450,000 per cubic millimeter; white cells, 11,800 per cubic millimeter, with 67% neutrophils, 27% lymphocytes, 1% monocytes, and 5% eosinophils. Hematocrit, 34%; platelet count, 18,000 per cubic millimeter; reticulocytes, 17.5%; bleeding time, 9 minutes; sedimentation rate, 75 mm. in one hour. The serum chloride, blood urea nitrogen, prothrombin time, and bilirubin were normal. Serum iron was 51μg. %. Occult blood examinations were consistently positive throughout the entire hospitalization. Roentgenological survey of the stomach, esophagus, colon, wrists, long bones, and skull revealed no abnormalities.

Skin testing for allergy was done. Sensitivity to egg and pork were considered to be positive.

Hospital Course.—His course in the hospital was accentuated by several bouts of upper respiratory infection and bilateral pneumonitis.

Eczema was treated by a replacement of milk with Nutramigen diet and topical hydrocortisone ointment. Improvement was noted.

On Oct. 22 cortisone therapy was begun. Eczema cleared well with the use of the large doses of cortisone, but thrombocytopenia, melena, petechiae, and progressive anemia persisted.

An abscess was noted on Jan. 3, 1957, in the perineal area. This was drained and culture revealed coagulase-positive Staphylococcus. Treat-

Fig. 2 (Case 6).—Age 31 months. Characteristic distribution of multiple large abscesses over entire body.

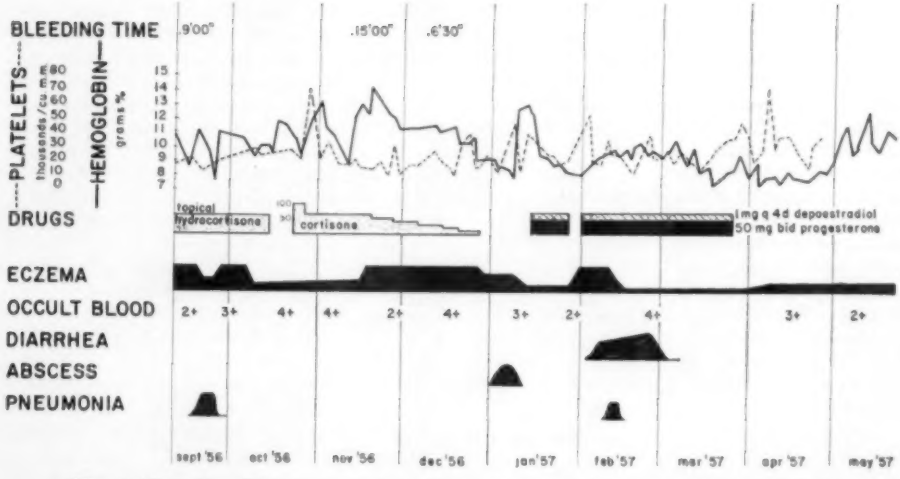

Fig. 3 (Case 6).—Clinical course from 11 to 19 months of age. Topical and parenteral cortisone and estrogen-progesterone therapies alleviated eczema slightly but did not affect thrombocytopenia, melena, or recurrent infections.

ment with erythromycin and drainage healed the abscess. Because of the reported response of certain skin lesions to combined therapy with estradiol cyclopentylpropionate (Depo-estradiol) and progesterone, treatment with these drugs was tried. Estradiol cyclopentylpropionate, 1 mg. q. 4 d., and progresterone, 50 mg. b. i. d., was given for two trial periods of two weeks each. Although each course of therapy resulted in definite improvement of the skin manifestations, there was persistence of the thrombocytopenia, melena, and anemia.

Intermittently because of recurrent melena, the child's hemoglobin fell to levels of 6 and 7 gm. He received several small transfusions.

Bone Marrow Biopsy.—Biopsy was done and revealed plasma layer of 65.1%, myeloid-erythroid layer of 6.9%. Normoblasts numbered 28.8%, and occasional macronormoblasts were seen. Neutrophils and precursors were 53.0%. Large aggregates of neutrophils were present. Eosinophils were 8.0%; basophils, 0.2%. Megakaryocytes appeared decreased in number, but platelets were present. Lymphoid cells numbered 10%, and plasma cells were present. Storage of iron appeared to be decreased.

Lymph Node Imprint.—A lymph node imprint was done, which revealed an increase in endothelial cells and macrophages, with evidence of phagocytis of erythrocytes and some hemosiderosis of the node.

There was increased amount of iron in the macrophages.

Clinical Course.—This patient had several episodes of severe bleeding from minimal trauma. The eczema continued unabated. Figure 2 demonstrates the massive subcutaneous abscesses that characteristically occur during the course of this disease.

This patient died at 32 months of age following an overwhelming herpes simplex infection. Autopsy revealed the same inflammatory changes and hemorrhages as the previous reports indicated.

CASE 7 (Fig. 4).—This 3-month-old white boy was admitted to the University of Minnesota Hospitals on Dec. 17, 1956.

Nine days after birth blood-streaked stools were noted. The melena lasted three weeks. Coincidental "thrush infection of the mouth" was noted. Three weeks prior to admission eczema was noted on the forehead and extremities. The diet had included breast feeding originally and later Nutramigen and S-M-A (preparation approximating mother's milk).

Physical Examination.—The infant was well developed and weighed 5.3 kg. There was minimal eczema of the face and extensor surfaces of the arms. The liver was palpable 2 cm. below the costal margin. The spleen was not palpable.

Laboratory Examination.—Hemoglobin was 8.7 gm. %; platelets were 26,000 per cubic millimeter; the white cell count was 16,200 per cubic millimeter, with a differential of 65% neutrophils, 18% lymphocytes, 6% monocytes, 9% eosinophils, and 2% basophils. Rumpel-Leede test was positive. Stool examination was positive for occult blood.

Hospital Course.—During the first two weeks, Nutramigen substitute was used. The eczema and thrombocytopenia continued. Two courses of progesterone, 50 mg. b. i. d., and estradiol cyclopentylpropionate, 1 mg. q. 4 d., were given for two

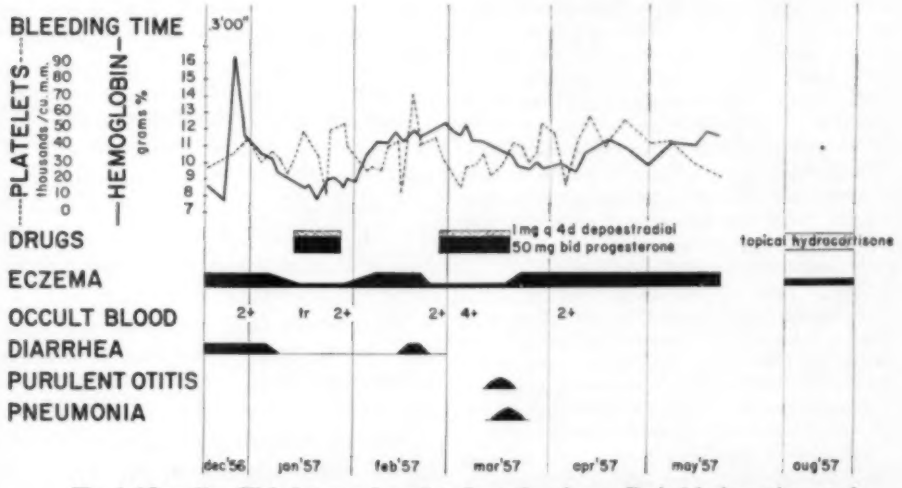

Fig. 4 (Case 6).—Clinical course from 3 to 8 months of age. Topical hydrocortisone and estrogen-progesterone therapy alleviated eczema slightly. Thrombocytopenia, melena, and recurrent infections continued unabated.

TABLE 1.—*Clinical Manifestations of Aldrich's Syndrome in Seven Patients*

Case	Age at Onset: Rectal Bleeding	Petechiae	Eczema	Purulent Otitis	Infections (Pneumonia or Abscess)	Platelets	Outcome
1	6 mo.	5 mo.	5 mo.	—	1 yr.	30,000	Died, 3 yr.; cerebral hemorrhage
2	—	3 day	2 mo.	—	1 yr.	168,000 (1X)	Died, 2 yr.; anemia, "heart failure"
3	1 day	1 yr.	1 yr.	7 mo.	3 mo.	28,000	Died; sepsis and thrombosis
4*	—	3 wk.	3 wk.	—	3 mo.	34,000	Died, 1 yr.; postsplenectomy and cortisone collapse
5	11 day	3 mo.	2 mo.	9 mo.	3 mo.	24,000	Died, 18 mo.; sepsis and pneumonia
6	6 day	4 mo.	3 mo.	9 mo.	6 mo.	14,000	Died, 32 mo.; herpes simplex
7	9 day	2 mo.	3 mo.	5 mo.	6 mo.	18,000	Died, 23 mo.; sepsis and pneumonia

* Severe bleeding from circumcision at five days of life.

weeks each. During both of these periods there was marked clearing of the eczema, but the melena and thrombocytopenia persisted.

Transfusion was given on Dec. 27 because of a marked fall in hemoglobin. Oral iron therapy was given in an attempt to maintain relatively normal hemoglobin without success.

Infections were present and consisted of bronchopneumonia, diarrhea, and draining purulent otitis. Proteus vulgaris was cultured from this purulent material, but no pathogens were obtained from the stools. Skin tests with egg white, milk, and wheat were positive.

The topical use of hydrocortisone ointment alleviated the severity of the eczema.

Roentgenological survey revealed no abnormalities of the skull and long bones.

Bone Marrow Aspiration.—Bone marrow aspiration demonstrated a normal myeloid-erythroid layer and normal cellularity. The normoblasts were 23.2%; neutrophils and precursors, 35.4%; eosinophils, 8.4%; basophils, 0.2%, and lymphoid cells, 32.8%. Plasma cells, macrophages, and osteoblasts were noted. The megakaryocytes were present in normal numbers, and platelet formation was normal.

Lymph Node Biopsy.—Biopsy of the left inguinal node was done. Normal architecture was present, and there were large collections of phagocytic cells and minimal reticular hyperplasia. Some of the macrophages contained pigmented lipid.

Clinical Course.—The eczema and thrombocytopenia continued unabated. He had had multiple massive subcutaneous abscesses similar to those seen in the other cases. Culture of these revealed β-hemolytic Staphylococcus pyogenes var. aureus. The organism was sensitive to erythromycin, and the skin lesions abated on erythromycin therapy.

Following an episode of diarrhea, skin infection and pneumonia, the patient died at 23 months of age. Autopsy findings were similar to previous observations in above cases.

Clinical Manifestations

In Table 1 are summarized the clinical features of this syndrome. In all but two of the cases, gross melena was present during the immediate neonatal period and was the first manifestation of the disease. In each of the cases, purpura has presented as petechiae and was noted early in life. Eczema was present in each of the cases and was similar in its distribution and morphological characteristics to atopic dermatitis of infancy. Otitis media, pyoderma, and pneumonia were the manifestations of infection regularly observed in these patients. The platelet count was pathologically depressed in every instance, save Case 2, in whom only one platelet count was observed. Although it was impossible to study this case thoroughly, the patient was a sibling of a child with the typical clinical and laboratory syndrome, and he himself showed eczema, purpura, and recurrent infection, with early death. We are thus forced to conclude that this patient suffered from Aldrich's syndrome, even though the solitary platelet count was not decreased.

The mortality from this disease was striking. At the time of this report all seven patients have died. Death was due to bleeding in two instances and to infection in five.

The consistently repeated pattern of early melena, thrombopenic purpura, eczematoid dermatitis, and recurrent sepsis indicate that each of these patients was suffering from

the syndrome originally described by Aldrich.

In Figure 1 the characteristic skin rash of one of the children with this syndrome is illustrated. The rash is characteristically distributed over the face, upper arms, and legs, with a relative sparing of the abdomen and back. In Figure 2 the characteristic multiple abscesses frequently observed in these patients are illustrated.

Figures 3 and 4 summarize the hospital course of the disease in Cases 6 and 7. The recurrent infections, persistent eczema, thrombopenia, and melena are illustrated. The failure of cortisone and the combined estrogen-progesterone therapy to affect the platelet count are apparent in the Figures. Some response of the eczema to both cortisone and the estrogen-progesterone regimen is indicated.

Familial Occurrence

One of the striking characteristics of this group of patients is the familial nature of this syndrome. In four of our cases, a positive familial history was obtained. In Patient 7, who was a member of the family previously described by Aldrich et al., in 1954, the genetic characteristics of a sex-linked recessive characteristic can now be extended along the lines that were originally predicted. In Figure 5, Case 7, we have used the same numbering system used in Aldrich's pedigree chart and have added the members of the large family born since that paper was published. In the additional data obtained there is excellent fulfillment of requirements for a sex-linked recessive trait. All of the new cases have been boys. Among the offspring of the two women, No. 16 and No. 24, half of the boys have developed the disease, but none of the girls have expressed this syndrome.

In Case 4 of our series, the family history was also extraordinary. The pedigree revealed that two male cousins of the propositus and a maternal uncle died of the syndrome. In addition, two male cousins

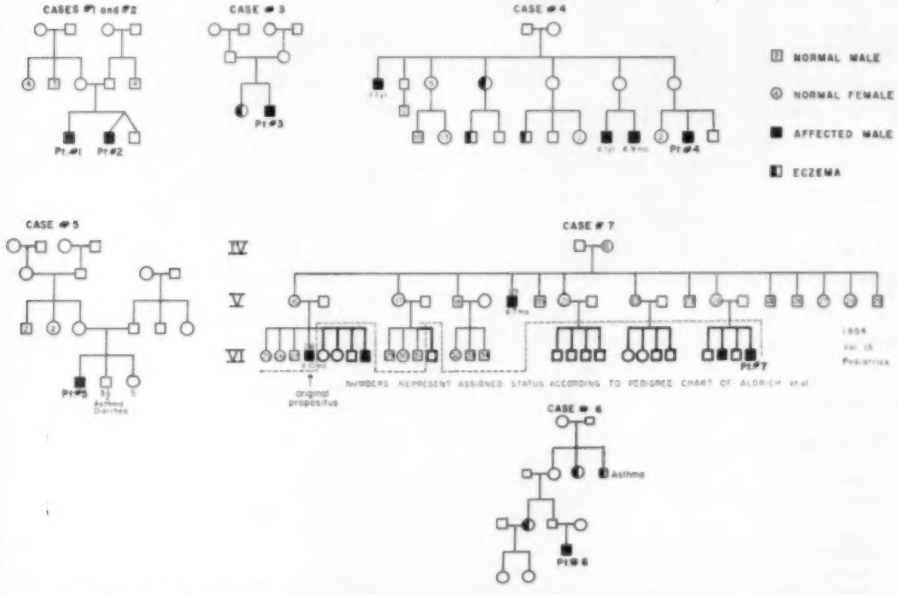

Fig. 5.—Genetic patterns of families in Cases 1 and 2 (upper left), 3 (upper middle), 4 (upper right), 5 (middle left), 7 (middle right), and 6 (lower) are presented. Note in Case 7 the hatched lines, which indicate the members added to the pedigree originally described by Aldrich.

suffered from severe eczema but did not have purpura. In these generations, none of 21 women suffered from this disease.

In one other family, multiple cases, Case 1 and Case 2 occurred in male siblings. It is of interest that a twin of Patient 2 did not suffer from the disease; it is thought that twin was fraternal.

Although none of the other members of the family in Cases 3, 5, and 6 have been affected, all of the patients with this disease have been boys.

In support of the original observation of Aldrich, we must conclude from genetic analysis of our material that Aldrich's syndrome is transmitted as a sex-linked recessive trait.

Immunological Investigation

Because of the high frequency of infection, the severity of infections when they did occur, and the paramount role of bacterial infection in the ultimate death of these patients, it was considered worth while to evaluate the known mechanisms of defense in these children. Consequently, the last two children were studied for their capacity to form agglutinating, complement-fixing, neutralizing, and antitoxic antibiotics. γ-Globulin concentrations were evaluated by electrophoretic techniques. The phagocytic capacity of the leukocytes and their motility was examined.[4,5] The morphological sequence of events in nonspecific inflammation was studied by the method of Rebuck.[6] The concentration of free properdin in the serum was also measured. In addition, the morphologic response of the bone marrow and regional lymph nodes to primary and secondary antigenic stimulation was evaluated. Finally, since Giedion and Scheidegger [7] have demonstrated that formation of isoagglutinins and certain other antibodies may be deficient even in the presence of normal γ-globulin concentrations, the blood type of each patient was determined and isoagglutinin titers against heterologous blood group antigens were measured.

Antibody Production and Response to Specific Antigens.—The antigens employed and the methods of stimulation were as follows. Immunization was provided by two injections at 15-day intervals of the following preparations: typhoid vaccine (Wyeth, 0.5 cc. subcutaneously) into the anterior medial aspect of the thigh, mumps vaccine (Lilly, 1 cc. intramuscularly), and diphtheria toxoid as combined diphtheria and tetanus toxoids with pertussis vaccine (Dip-Per-Tet, Cutter; 0.5 cc. intramuscularly). In addition, commercial Lilly poliomyelitis vaccine was injected on four occasions (an initial injection at 0 days, second injection 15 days later, and an additional two injections five months later). Serial determinations of the response was obtained by blood samples taken at weekly intervals for the first month after the initial injection.

The immune responses obtained are summarized in Table 2. Patient 7 showed an adequate formation of agglutinins against

TABLE 2.—*Study of Immunological Response in Patients with Aldrich's Syndrome*

	Case 7			Case 6		
Antigen Injected	**H**	**O**	**B**	**H**	**O**	**B**
Typhoid agglutination						
Before	1:80	0	1:160	0	0	0
After	1:2560	1:1280	1:1280	1:2560	1:1280	0
Mumps complement-fixation						
Before	Negative			Negative		
After	1:256			1:8		
Diphtheria antitoxin titration, μ/cc.						
Before	<0.0075			<0.01		
After	1.0			<0.01		
Poliomyelitis vaccine	**I**	**II**	**III**	**I**	**II**	**III**
Before	<1:4	<1:4	<1:4	<1:4	<1:4	<1:4
After	<1:4	1:4	1:4	<1:4	<1:4	<1:4

typhoid H, O, and B antigens, complement-fixing antibodies against mumps, and antitoxic antibodies directed against diphtheria toxin. On the other hand, Patient 6 had an excellent immune response to typhoid H and O antigens but no response to B antigens. The serum was anticomplementary, and so tests for complement-fixing antibodies against mumps were unsuccessful. However, no demonstrable response to diphtheria toxoid was obtained. In neither patient were antibody responses to polio vaccine obtained.

Fig. 6.—Electrophoretic serum patterns of patients with Aldrich's syndrome. *A*, Case 3. *B*, Case 4. *C*, Case 5. *D*, Case 6. *E*, Case 7.

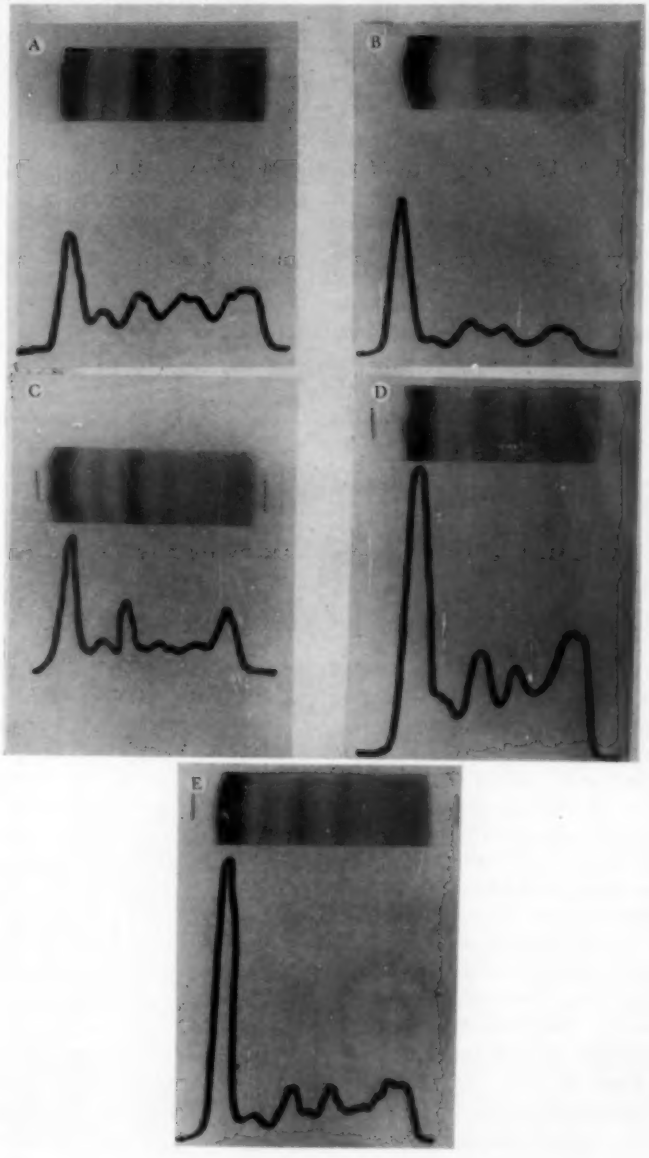

TABLE 3.—*Serum Protein Fractionation in Patients with Aldrich's Syndrome*

Case	Albumin * (3.9±0.5)	Globulins * α_1 (0.2±0.1)	α_2 (0.6±0.1)	β (0.9±0.2)	γ (1.1±0.3)
3	1.7	0.5	1.0	1.5	1.2
4	3.6	0.2	1.2	0.97	1.0
5	1.8	0.4	1.0	0.5	1.0
6	3.3	0.2	0.8	0.6	1.5
7	3.7	0.3	0.7	0.6	1.4

* Numbers in parentheses are normal values.

TABLE 4.—*Pierce-Martin Study of Migratory Capacity of Leukocytes in Patients with Aldrich's Syndrome*

Test System	Case 6	Case 7
Patients' cells, patients' plasma	1.0 *	1.1
Patients' cells, control plasma	0.97	3.1
Control cells, patients' plasma	1.05	1.2
Control cells, control plasma	1.05	0.9
Average migration of normal leukocytes (20 determinations)	1.2	

* Figures indicate millimeters of migration per 8-hour period.

γ-*Globulin.*—In Figure 6 are illustrated electrophoretic patterns on five of these patients, and in Table 3 are summarized the data on composition of the serum proteins in each case. In none were any of the protein fractions absent or grossly deficient from the sera. Four of the five, however, had a slight increase in the γ-globulin fraction, and all four of these also had a relative and absolute increase in the α_2 component. It seems clear that the susceptibility of these patients to infection cannot be explained on the basis of a γ-globulin deficiency.

Studies of the Motility of Leukocytes.—In another effort to evaluate defense function in these patients, the migratory capacity of the leukocytes was observed by the technique of Martin et al.,[5] as previously modified in our laboratory.[6]

Patient 6 showed the same magnitude of migration of leukocytes from the buffy coat when the patient's cells were kept with the patient's own plasma, when patient's cells were combined with control plasma, when control cells were placed in patient's plasma, and when control cells were kept in control plasma. In the case of Patient 7, exactly the same results were obtained, except that when the patient's cells were combined with control plasma the total migration of leukocytes was approximately three times farther than in any other combination. No explanation for this abnormal observation was apparent. Results of the study are summarized in Table 4.

Surface Phagocytosis by Neutrophils.—Phagocytic capacity of neutrophils are summarized in Table 5. In these tests, the capacity of the patient's cells in the patient's own plasma were compared to the phagocytic activity of the patient's cells in normal plasma, of normal control leukocytes in control plasma, and of normal control cells in the patient's plasma. Phagocytosis of a rough strain of Type I pneumococci was evaluated by a method previously described. In neither case was a deficiency of phagocytic capacity or an excessive phagocytosis observed.

TABLE 5.—*Study of Surface Phagocytosis by Leukocytes of Pneumoccocus (Rough) in Patients with Aldrich's Syndrome*

Test System	Case 6	Case 7 *
Patients' cells, patients' plasma	101 †	31.3 †
Patients' cells, control plasma	98	35.5
Control cells, control plasma	106	36.3
Control cells, patients' plasma	104	37.7

* Carried out at different time with different rough strain pneumococcus.

† Mean number of pneumococci phagocytized per cell.

Morphology of the Inflammatory Response.—The capacity of Patients 6 and 7 to develop a nonspecific inflammatory response was studied by the method of Rebuck.[6] With this system both patients showed the initial migration of histogenous mononuclear cells into the area of inflammation and the appearance of polymorphonuclear leukocytes at the inflammatory site within one hour after trauma to the skin. These changes were succeeded in turn by

the appearance of hematogenous lymphocytes or monocytes in the exudate within six hours after trauma and by the progressive development of these cells to hematogenous macrophages by the time of the 14-hour sample. No significant difference between the patients of this group and normal persons studied in this manner was observed.

Free Properdin Concentration in the Serum.—Another possible basis for increased susceptibility to infection which was considered in these patients was the serum properdin concentration. Summarized in Table 6 are compared values of free properdin observed in the serum of all patients and those obtained in normal persons. As may be seen in the Table, the properdin values in the two patients studied fell well within the normal limits obtained in Dr. Pillemer's laboratory.

TABLE 6.—*Serum Properdin Concentration* *

	Units
Case 6	4
Case 7	8
Mean	6
Normal range	2-10

* The late Dr. Louis Pillemer determined properdin concentrations and supplied mean values and ranges obtained in normal persons.

Lymph Node Response to Antigenic Stimulation.—After previous stimulation with typhoid paratyphoid antigen, two of the patients were given injections subcutaneously into the anterior medial aspect of the right thigh of 0.5 cc. of commercial typhoid A and B vaccine (Wyeth). Four days later the right inguinal lymph nodes draining the areas of injection were excised. Imprints of the nodes were made, and sections were stained with hematoxylin and eosin and with methyl green-pyronin. These nodes showed a thick active cortex containing both primary and secondary nodules. In addition, the medullary cords were filled with clusters of plasma cells. Thus, the morphological response to antigenic stimulation was found to be no different from that observed in normal persons. The plasmacytic response of the regional lymph nodes is illustrated in Figure 7 (methyl green-pyronin).

Measurement of Natural Isoagglutinins.—The blood type of each patient was determined and isoagglutinins measured against heterologous blood group. The antibodies were sought in standard saline dilutions. As is shown in Table 7, all of these patients were of blood Groups A and B. None of the patients studied possessed isoagglutinins

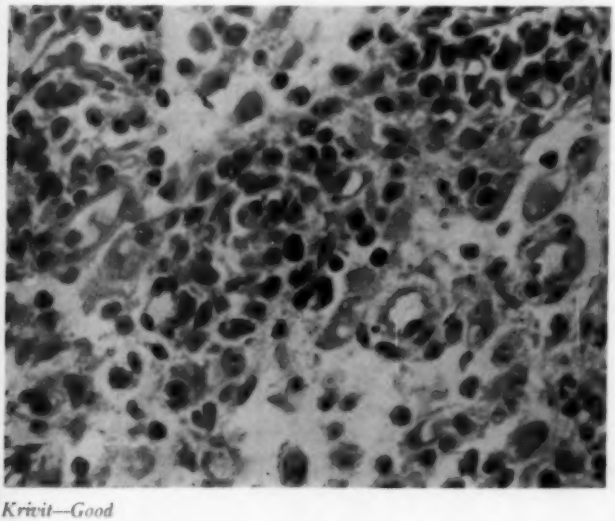

Fig. 7.—Lymph node response to antigenic stimulation following typhoid A and B injection (methyl green-pyronin stain). Note clusters of plasma cells.

TABLE 7.—*Natural Isoagglutinins in Patients with Aldrich's Syndrome and Controls*

Case	Blood Group	Age, Mo.	Isoagglutins	
			Anti-A	Anti-B
3	A	7		Negative
4	B	12	Negative	
5	A	7		Negative
6	B	31	1:2	
7	A	18		Negative
Controls				
A	A	8		1:10
B	A	10		1:10
C	A	11		1:20
D	A	12		1:10
E	A	15		1:640
F	A	24		1:20
G	A	36		1:5
H	A	7		1:2
I	A	8½		1:2
J	A	17		1:2
K	A	20		Negative
L	A	24		1:5
M	A	24		Negative
N	B	24	1:80	
O	B	36	1:640	

against heterologous blood group antigens above a titer of 1:2.

As a control the natural isoagglutinins were determined in 13 other infants and children who had blood Group A. The age ranged from 7 months to 36 months. Two of these had no isoagglutinins, and five had titers of 1:5 or less. In two blood Group B patients, natural isoagglutinins were found.

Studies of Adrenal Functions

Since it is possible that disturbances in adrenal function might be associated with enhanced susceptibility to infection, a study of adrenal function was made with these patients. In Patient 6 the fasting plasma level of 17-hydroxycorticosteroid, measured by the method of Nelson and Samuels, was 9.2μg. per 100 cc. on one occasion. Two hours after corticotropin (ACTH) injection, the circulating 17-hydroxycorticosteroid level was 43μg. per 100 cc. In Patient 7 a fasting level of 17-hydroxycorticosteroid was 15.1μg. per 100 cc.; four hours after intramuscular injection of 25 units of corticotropin (ACTH), the level reached 49.5μg. per 100 cc. The 24-hour urinary excretion of 17-ketosteroids was 0.5 mg. per 24 hours; the urinary excretion of 17-hydroxycorticosteroids measured 2.8 mg. per 24 hours. We interpret these meager data as being consistent with the view that adrenal function in these patients is normal.

Platelet Studies

The platelet counts in the peripheral blood were uniformly low. Bone marrow studies revealed at least a normal number of megakaryocytes in all samples. In most of the patients the morphology of the megakaryocytes and platelet production by these cells appeared to be normal. In one patient, Patient 4, a developmental arrest of the megakaryocytes was described. No platelet agglutinins could be demonstrated in the serum upon study in our laboratories, and Dr. Tullis* performed platelet agglutinin studies by his technique, which he also reported as being negative in Patients 6 and 7.

Pathology

Lymph node and skin biopsy specimens and spleen and autopsy material were available from five of the seven reported cases. In each of the cases, the lymph nodes demonstrated a nonspecific generalized benign hyperplasia. The reticulum was increased in amount, and there was marked proliferation of primary and secondary follicles. In the spleen and lymph nodes, evidence of erythrophagocytosis was present, but there was only minimal sinusoidal engorgement with red cells. No massive infiltration of sheets or nodules of mononuclear cells was seen, and the architecture of the lymphoid tissues was preserved. It was the conclusion of the pathologist that the lymphoid tissue did not reveal evidence of malignant reticuloendothelial disease such as is observed in Letterer-Siwe's disease, Hand-Schuller Christian's disease, and related disorders. The morphological description of the lym-

*Dr. James Tullis, Blood Preservation and Characterization Laboratories, Harvard University, Cambridge, Mass.

phoid tissue in each instance was "benign lymphoid hyperplasia."

Skin biopsy revealed no nodular mononuclear type infiltration but rather evidence of marked inflammatory reaction and hemorrhage of nonspecific type. Minute superficial abscess formations were sometimes present.

Examination of the thymus revealed no characteristic abnormalities.

In one patient, Patient 3, who died of staphylococcal sepsis, thrombotic lesions were found in the small arterioles in the kidneys, lungs, and pancreas. These lesions were reminiscent of those observed in thrombotic thrombocytopenic purpura. In one of the other patients, a single thrombotic lesion of the same type was observed in a small arteriole of a cervical lymph node obtained at biopsy.

The other findings on the autopsy studies reflected the pulmonary and generalized infections of which these patients died.

Comment

The clinical association of thrombocytopenia, eczema, and recurrent infection has been previously described by Aldrich, Steinberg, and Campbell [1]; Huntely and Dees,[2] and Wolff and Bertucio.[3] The common clinical features in these cases, the evidence of a sex-linked recessive hereditary pattern, the inordinate susceptibility to infection, and the almost uniformly fatal outcome suggest that this is a definite syndrome.

The presence of blood per rectum has been the first abnormality noted in five of the seven patients presented here. This presenting symptom was not mentioned in the case reports of Huntely and Wolff but was observed in the cases described by Aldrich. The presence of petechia in the first two to three months of life would suggest that these hemorrhagic episodes are usually the original signs of this disorder.

The thrombotic lesions present in two of the patients studied are intriguing as a possible cause for the platelet deficiency. In Patient 3 these were generalized enough to have been of significance in the utilization of the platelets, but it seems likely that the thrombotic process occurred during the last several days of life of this patient and was a consequence of the terminal sepsis. It seems unlikely that the process resulting in these lesions was present during the long clinical course in this patient without producing overt renal disease and renal parenchymal failure. The thrombotic lesion in Patient 5 was confined to only one lymph node and can hardly be considered to be of significance as a process responsible for the low platelet levels.

The eczema observed in these patients is similar to infantile atopic eczema in many respects. The areas of predilection are the same and the appearance of lesions do not differ significantly from those observed in atopic eczema. Furthermore, skin tests for sensitivity were frequently positive for wheat, eggs, and milk. However, the failure of elimination diets to alter the course or even the skin lesions of these patients is evidence against the hypothesis that allergy to cow's milk plays an important role in this disease. The observation of Huntely and Dees that the patients having this syndrome who have been subjected to splenectomy often die suddenly from sepsis dramatically emphasizes the increased frequency and severity of infection in these cases. Similarly, our patient whom we splenectomized at 8 months of age died from an apparently overwhelming infection two months later. The consistency of this pattern in other reported cases in conjunction with the increased frequency of infections, even in the nonsplenectomized patients, made us reluctant to perform splenectomy in these patients and directed our attention to the defense mechanisms. An extensive study of known mechanisms of defense against infection, however, was revealing only in that these patients lacked isoagglutinins against heterologous blood group cells. The uniform lack of isoagglutinins may be an immunological anomaly in these patients which will require further investigation.

The observations of Giedion and Scheidegger [7] indicating that congenital anomalies in immunological mechanism may occur in the presence of normal serum concentrations of γ-globulin suggest that further studies of the serums of these children with use of the immunoelectrophoretic technique may be fruitful. This observation must be interpreted with caution, since Hitzig [9] has observed that the β_2A and β_2M globulins which were associated with the absence of isoagglutinins in Giedion and Scheidegger's study are normally lacking in young infants. All of these patients had normal or increased concentrations of γ-globulin. The last two patients had normal concentration of properdin, formed antibody, and plasma cells in response to antigenic stimulation and possessed normal leukocytes capable of known migration, phagocytosis, and participation in the inflammatory response.

The use of progesterone and estrogen, according to the regimen suggested by Good [10] for treatment of epidermolysis bullosa, produced significant improvement in the skin disease but had no effect on the thrombopenia. The regimen was not tried for a sufficient time to determine whether or not it had any effect on resistance to infection.

As we studied these cases, a similarity to the syndrome of nonlipid histocytosis or Letterer-Siwe's disease frequently came to mind. However, critical comparison of the two syndromes revealed consistent differences. For example, disease in our patients regularly began with melena in the neonatal period, a manifestion which is both uncommon and of late occurrence in Letterer-Siwe's disease. Our patients had an atopic type of dermatitis and never had the characteristic hemorrhagic maculopapular rash of Letterer-Siwe's disease. Further, the lymphadenopathy, splenomegaly, and osseous lesions of the malignant reticuloendothelioses were not seen in our patients. Finally, the strongly positive family history in our cases does not occur in Letterer-Siwe's disease, and the pathology of the lymphoid tissue is entirely different in the two syndromes.

Summary

The clinical, hematological, and pathological characteristics in Aldrich's syndrome (thrombocytopenia, eczema, and infection) are reviewed, and seven new cases are presented. All of our patients were boys; the syndrome appears to be transmitted as a sex-linked recessive trait.

The typical onset of melena in the neonatal period was noted in five of the affected children.

The persistent thrombocytopenia and normal numbers and morphology of megakaryocytes was observed. Peripheral and marrow eosinophilia was noted. Further, the bone marrow examinations, except for revealing a mild plasmacytosis and toxic changes among the neutrophils, were normal. Nonspecific inflammatory changes were noted in the skin and lymph node biopsy specimens. However, postmortem material in Patient 3 and lymph node biopsy in Patient 5 revealed multiple thromboses of small arterioles.

A fatal outcome was noted in all of the patients despite cortisone and corticotropin (ACTH) therapy followed by splenectomy in one patient and despite multiple types of antiallergic therapy in the others.

Because of the frequency and severity of infections noted, an investigation of defense mechanisms was made. This revealed no clear evidence of deficiency of the immune response to most antigens. The isoagglutinins were regularly absent in these children. γ-Globulin levels were normal or slightly elevated. Properdin levels were normal. Leukocyte function in the inflammatory reaction, migration, and phagocytosis were within normal limits.

The etiology of the thrombocytopenia was studied. No platelet agglutinins were noted. Normal production of platelets was apparent. The thrombocytopenia did not demonstrate any relation to the course of the eczema.

Adrenal steroid physiology was studied, and normal circulating plasma 17-hydroxycorticosteroids were present. Also the response of 17-hydroxycorticosteroids levels to stimulation with corticotropin were normal.

All attempts at treatment of the disease have been unsuccessful, though both adrenal steroid therapy and systemic treatment with estrogen and progesterone ameliorated the eczematoid processes.

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Familial Addison's Disease

Case Reports of Two Sisters with Corticoid Deficiency Unassociated with Hypoaldosteronism

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Although familial Addison's disease has been previously reported, it is usually associated with hypoparathyroidism or with congenital adrenal hyperplasia. Familial Addison's disease by itself is rare. Recent case reports by Whitaker et al.[1] and DiGeorge and Paschkis [2] have reviewed the subject of hypoparathyroidism and Addison's disease. The Addisonian-like aspect of the familial disease, congenital adrenal hyperplasia, has been reviewed by Iversen,[3] Grumbach and Wilkins,[4] and Childs et al.[5]

Reports of familial Addison's disease have been reviewed. Fleming and Miller [6] and Croom,[7] in 1900 and 1909, respectively, reported family members who were weak and pigmented and who were felt on the basis of clinical observation to have Addison's disease. Rolleston [8] mentions the syndrome as occurring in two sisters. Smith and Higgins [9] diagnosed the disease in two brothers because of pigmentation and decreased serum sodium. Wakefield and Smith [10] reported an excessively pigmented man who at autopsy had adrenal atrophy, possibly secondary to "vascular degeneration" of the anterior pituitary. A number of his relatives were hyperpigmented but healthy. Briggs et al.[11] reported two brothers with pigmentation, salt craving, and a chemical picture suggestive of hypoadrenalcorticism. At autopsy one of these patients revealed cortical atrophy but the pituitary was normal.

This report is of two sisters who in their second year of life developed hyperpigmentation, weakness, and later convulsions. One child was studied by postmortem examination, and the other, who is living, is reported from the aspects of clinical and laboratory diagnosis. Particular emphasis has been placed on the presence of mineralcorticoid activity in the absence of other corticoid activity, an unusual finding in patients with Addison's disease.

Report of Cases

CASE 1.—This girl died at 30 months of age, after the onset of hyperpigmentation, weakness, and convulsions. Detailed clinical studies were not carried out.

She was entirely well until the age of 10 months, when recurrent attacks of tonsillitis commenced. After the first year she had a gradual onset of muscular weakness and increasing pigmentation. When she was 19 months of age a tonsillectomy was performed, after which she was treated because of coma and dehydration. From this time on she began to have convulsions associated with fever. At the age of 2 years she was readmitted to the hospital in a comatose state after an attack of gastroenteritis. After six days of fluid therapy she recovered. A lumbar puncture performed on the first hospital day revealed no increase in cells or protein. During the next six months she became so weak that she was unable to walk. Finally, when she was 30 months of age, she was readmitted with convulsions and coma and she died within 12 hours.

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The aldosterone determinations were supervised by Dr. John Leutscher, and the blood corticoid determinations were supervised by Dr. Vincent Kelly. Dr. Richard Koch made available the initial laboratory studies performed in Case 2.

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The convulsions could not definitely be associated with fasting. Serum electrolytes were not measured, and no special adrenal function tests were done. She had never had craving for salt.

The parents remarked that the time and sequence of onset of the pigmentation, weakness, and convulsions were remarkably similar to those of her sister (Case 2). Both children were large for their age.

Autopsy Findings.—Gross Description: The body was that of a well-developed well-nourished white girl. The body length was 104 cm. (normal 91.4 cm.) and the body weight, approximately 16.5 kg. The lips were cyanotic and dry. The thyroid was not enlarged. The external genitalia were those of a normal female child. The extremities showed no masses or deformities. The skin was dark bronze in color. There was a 1.9 cm. layer of yellow lobulated subcutaneous fat present at the level of the umbilicus. There was some enlargement of mesenteric lymph nodes; examination of the other peritoneal structures revealed their size, location, and consistency to be normal. The pelvic viscera were also unremarkable. The heart appeared normal, and the left ventricle measured 0.4 cm. in average thickness. The brain was grossly and microscopically within normal limits. Both the right and the left adrenal glands were difficult to identify. They had a slightly purple-gray color and were extremely thin and membranous. They were "shell-like" and resembled the connective tissue in the surrounding area. Only a fine line of cortical tissue was evident.

The weights of the organs were as follows:

	Gm.	Normal (for Her Height), Gm.
Heart	80	73
Lung, R.	190	90
Lung, L.	160	85
Kidney, R.	60	58
Kidney, L.	60	56
Spleen	60	39
Liver	550	516
Thymus	35	
Brain	1,450	1,191
Adrenals (Unable to weigh)		2-7

Adrenal Glands: Sections of the adrenal glands showed marked atrophy of cortical tissue (Fig. 1). The capsule was relatively thick and was of fibrous composition. Only occasional clumps of cortical cells remained in the zona glomerulosa. All cells of the zonae fasiculata and reticularis were absent. Chromaffin cells of the medulla were present and, in fact, appeared fairly abundant and well preserved. Between this tissue and the few cortical cells remaining there were a few pigment-laden macrophage cells and in some areas fair quantities of loose, and at times compact, fibrous connective tissue. Engorged capillaries and a few minute foci of hemorrhage occurred here. The central vein was not thrombosed.

Enlarged Lymph Nodes: Sections showed only hyperplasia.

Lungs: Sections showed extensive homogeneous pink edema fluid in alveoli and sometimes in interstitial tissue between lung lobules, as well as intense engorgement of capillaries. There was no pneumonitis.

Spleen: Sections showed only follicular hyperplasia of Malpighian bodies.

Pituitary Gland: The pituitary, in hematoxylin-and-eosin-stained sections, was largely composed of small cells with pale cytoplasm, more opaque and more abundant than that of true chromophobe cells, indicating that the dominant cell was a small amphophil. These cells did show variation in

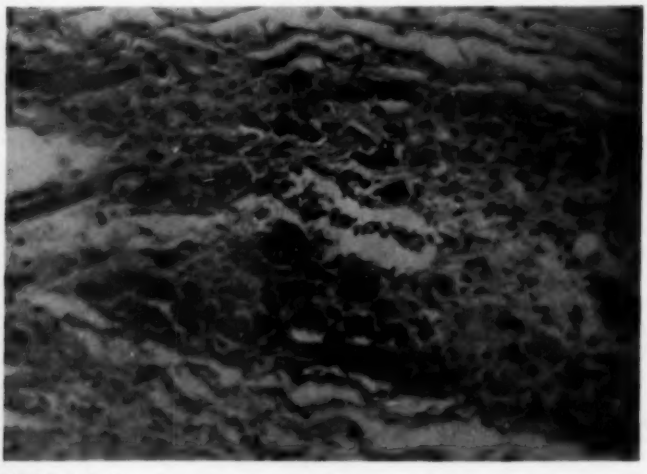

Fig. 1 (Case 1).— Histology of adrenal cortex.

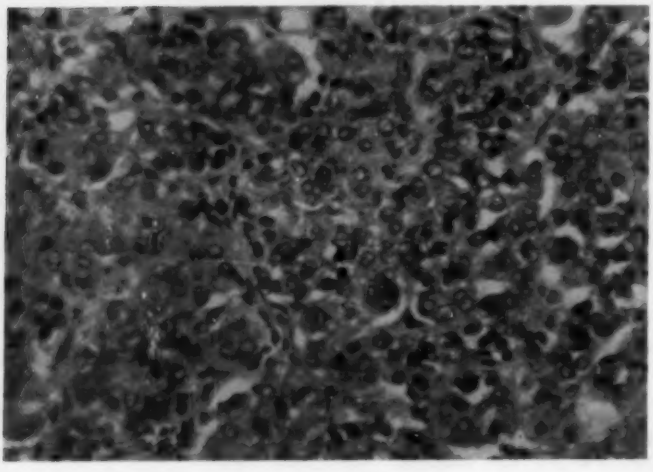

Fig. 2 (Case 1).—Histology of anterior pituitary.

nuclear size and shape, but none of the cells were truly "hypertrophic amphophils." In hematoxylin and eosin sections and with the phosphotungstic acid-hematoxylin stain a small number of acidophil cells was demonstrated, and rare basophil cells were seen in sections stained by the periodic acid-leukofuchsin, direct aldehyde-fuchsin, and sulfuric acid-permanganate aldehyde-fuchsin procedures. No cells with cytoplasmic character suggesting that of Crooke's hyaline change were seen. Posterior pituitary was not available for microscopic study. No evidences of inflammation, fibrosis, or other acquired destructive process was seen in the pituitary.

Case 2.—The sister of Patient 1 was in good health until the age of one year, when she had the gradual onset of hyperpigmentation and weakness which was later followed by convulsions. Laboratory tests supported the diagnosis of Addison's disease, but no electrolyte abnormality was present.

The pregnancy and delivery were normal except for a mild preeclampsia. The birth weight was 3,550 gm. A twin boy has been entirely well. A daughter by the mother's first husband had acute rheumatic fever, but otherwise the family history is not remarkable. From the age of 18 months her weakness was pronounced and her unsteadiness caused her to crawl when climbing or descending the stairs. Although her parents were fairly dark skinned and of Italian extraction, her pigmentation was much more marked. When she was 3 years of age an uncomplicated tonsillectomy was performed because of recurrent tonsillitis.

At the age of 3 years 4 months, after a two-day automobile trip during which she subsisted mostly on candy bars, she became listless and complained of abdominal pain. While in a hospital waiting room she became unconscious and had a convulsion. At that time the blood sugar was 10 mg. %. Pertinent laboratory studies in another hospital revealed that the electrolytes were constantly normal, but she failed to show any eosinophil, blood corticoid, or urinary 17-ketosteroid response to daily administration of intramuscular corticotropin (Table 1). Oral cortisone (total daily dose 12.5 mg.) resulted in an increase in

Table 1.—*Steroid Values*

Age, Yr.	Blood Corticoids, * μg/100 Ml.	Urinary 17-Ketosteroids, Mg/24 hr.	Urinary Aldosterone, μg/24 hr.	Treatment and Comment
3 4/12	3.4			None
	6.2	0.2		After 3 days of I. M. corticotropin
3 6/12	0	0.7		No oral cortisone for 12 hr.
	0			After 4 hr. of I. V. corticotropin (noon)
	0			After 7 days of I. V. corticotropin
3 10/12			2.7	Average Na intake
			7.9	2d day of Na-free diet
4 7/12	4.8			While receiving 50 mg. of I. M. cortisone q. 3 d.
	138.4			After 7 days of I. M. corticotropin
4 11/12	0			No therapy for 2 wk.
	0			After 4 hr. of I. V. corticotropin (noon)
	0			After 6 days of I. M. corticotropin

* Specimens drawn between 8 and 9 a. m. unless otherwise noted.

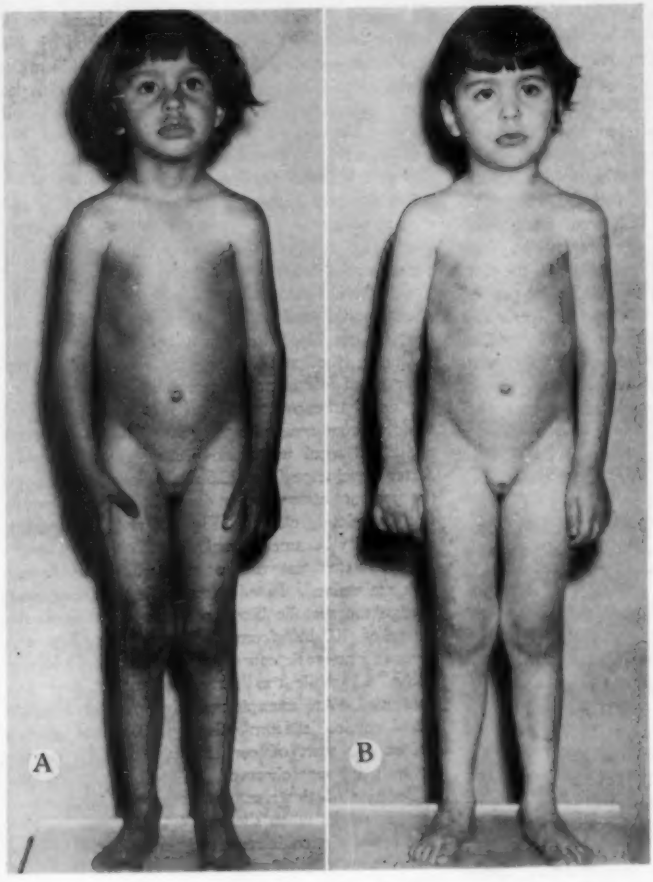

Fig. 3 (Case 2).—*A*, hyperpigmentation while on oral cortisone, 12 mg. per day, *B*, lack of hyperpigmentation while receiving cortisone, 50 mg. intramuscularly every third day.

strength and slight fading of the hyperpigmentation.

She had at no time had salt or carbohydrate craving. There had never been any dizziness.

She was first seen by one of us at the age of 3 years 5 months, one month after institution of cortisone therapy. She was chronically ill and deeply pigmented (Fig. 3). The blood pressure was 84/0 in the supine and 70/0 in the sitting position. The measurements are recorded in Table 2. She was of average height for a 4½-year-old girl. Her proportions as judged by facial maturation and lower segment length were more advanced and closer to those of a 7- or 8-year-old girl. The trunk appeared long and narrow, due in part to the smallness of her pectoralis muscles. Her grip was weak. The subcutaneous fat was less than average for her size but of good turgor. The skin was dark brown in all areas. The knuckles, gums, and creases in the palmar surfaces of the hands were deeply pigmented. There was no sign of oral or skin moniliasis. Her sexual development was normally immature, and the clitoris was approximately 0.4 cm. in length.

On July 1, 1956 (age 3 years 6 months), while still ingesting 12.5 mg. (two 5 mg. and one 2.5

TABLE 2.—*Physical Examination Data*

	Case 1	Case 2	
Age	2 6/12	3 5/12	4 10/12
Height	104 cm. (L 97) *	106.4 cm. (97%) *	117 cm.
Weight	16.5 kg. (90th) *	16.3 kg. (75%) *	19.7 kg.
Span		106 cm.	
Lower seg.		51.8 cm.	54.9 cm.
Head cir.		50 cm.	50.5 cm.
Chest cir.		54 cm.	57.0 cm.
Abd. cir.		52 cm.	53.0 cm.

* Refers to percentile standing according to data of Stuart and Meredith.[14]

mg. doses) of cortisone daily, she had a generalized convulsion associated with the onset of fever and sore throat. The seizure occurred approximately 15 minutes after ingestion of a cup of cocoa. A blood sugar specimen was not obtained.

During the hospital admission that followed, certain additional laboratory work was obtained. The heart size was normal radiographically, and no calcifications were seen in the abdomen. The tuberculin and histoplasmin skin tests were negative. An average osseous development of four years was suggested by the presence of the following epiphyseal centers: proximal fibula, patella, all three cuneiforms, and four carpal centers. The epiphyseal centers of the proximal radius, trapezium, scaphoid, and greater trochanter were absent. The serum electrolytes, blood urea, nitrogen, calcium (10.1 mg. %), phosphorus (5.3 mg. %), alkaline phosphatase (11.3 Bodansky units), and several fasting blood sugars were normal. The protein-bound iodine was 9.3μg. per 100 ml. of plasma.

Studies to determine the function of the adrenal cortex as regards production of 17-hydroxycorticosterone (Compound F) were carried out one day after omitting the small oral dose of cortisone. The glucose tolerance curve and two insulin tolerance curves are represented in Figure 4. The Robinson-Power-Kepler test [12] was positive in that her night urine volume (124 ml.) exceeded the highest hourly urine volume (109 ml.) following the water load. The electrolyte portion of the test was within normal limits (Factor A=95). Blood corticoids were zero before and after intravenous corticotropin and after six days of intramuscular corticotropin (40 units per day) (Table 1). During the six days of corticotropin the blood eosinophils did not drop (166 per cubic millimeter on the sixth day).

Because she had never had salt craving or abnormal serum electrolytes the production of aldosterone could be studied in detail without fear of crisis. Consequently she was placed on a sodium-free diet for six days. At the end of this period her serum sodium had dropped to 128 mEq. per liter and her urinary sodium, to 2 mEq. per liter; no untoward effects occurred. The total urinary aldosterone four months later while she was on a regular diet was 2.7μg., and on the second day of a sodium-free diet it was 7.9μg.

On discharge from the hospital she was placed on intramuscular cortisone, 50 mg. every third day (16.6 mg. per day). Four days after this regimen was started she again had a generalized tonic convulsion 15 minutes after a breakfast of sugar, milk, and cereal. On admission to the hospital her blood sugar was 112 mg. %.

During the past 22 months she has received 50 mg. of cortisone intramuscularly every third day and has encountered several respiratory infections without unusual symptoms. The mother adds additional oral cortisone during these periods. After the change from 12.5 mg. of oral cortisone to the present intramuscular dose, the hyperpigmentation completely cleared (Fig. 3), and her strength and activity became normal. The Robinson-Power-Kepler water test was normal while this dosage was maintained. In addition, with the increase in dosage the systolic blood pressure went up to the range of 100-110 from 80-85 mm. Hg. She was given a one-week course of corticotropin (40 mg. gel q. d.) while the intramuscular cortisone was continued. An unexplained rise of the 8 a. m. blood corticoids from 4.8 per 100 ml. of plasma before the start of corticotropin to 138.4 on the seventh day was observed.

Because of the rise, cortisone was discontinued for six weeks when she was 4 11/12 years of age. The blood corticoids remained zero after 40 units of intravenous corticotropin (ACTH), and after six days of intramuscular corticotropin. In addition, weakness, hyperpigmentation, hypotension, and weight loss reappeared. Accordingly, cortisone was restarted.

With use of fluorochromed rabbit antihuman γ-globulin, antiadrenal antibody in the patient's serum was not demonstrated.

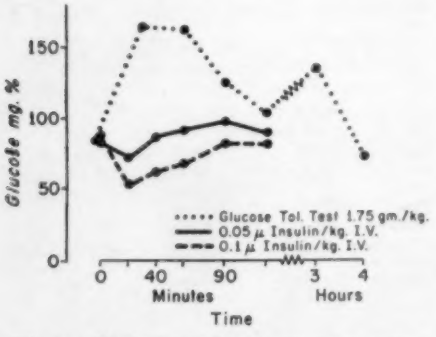

Fig. 4.—Glucose and insulin tolerance tests.

Comment

It is very probable that these two sisters illustrate the same disease process. Because of the rarity of idiopathic juvenile Addison's disease, it is almost inconceivable that two cases would occur by chance in the same family. Their clinical histories are similar in that the state of health during the first year was normal and the gradual onset of pigmentation and muscular weakness occurred in the second year. The ab-

sence of salt craving and the convulsions are also identical. Both girls were abnormally tall. In addition, the autopsy findings in the older sister correspond closely with what would be expected in the younger sister on the basis of her clinical studies. Accordingly, the discussion to follow will be based on the assumption that they have the same disease process.

For the sake of clarity, the adrenal cortex can be discussed in regard to three special activities: (*a*) aldosterone, (*b*) corticoid, and (*c*) androgen. These children do not have the classical form of Addison's disease in that the electrolyte-regulating mechanism (aldosterone) of the adrenal cortex is functioning. There was, however, clear-cut evidence of corticoid deficiency. Androgenic activity cannot be completely evaluated at this age.

(*a*) *Aldosterone Activity.*—The ability of the younger sister to conserve urinary sodium and the presence of normal urinary aldosterone, coupled with the presence of the remaining zona glomerulosa in the older sister, suggests that the electrolyte-regulating ability is still present. The presumptive evidence that the glomerulosa is related to electrolyte regulation was developed in animals by Deane [13] and by Sanger and Stack-Dunn,[15] and similar conclusions have been reached for man. In addition, atrophy of the zonae fasciculata and reticularis fails to occur in hyperaldosteronism.[16]

(*b*) *Corticoid Activity.*—Corticoid deficiency was demonstrated in Patient 2 by the inability of corticotropin to increase blood corticoid.[17] Failure of gluconeogenesis was probably the cause for her original hypoglycemic convulsion. The two subsequent convulsions cannot be adequately explained by this mechanism because she had recently ingested carbohydrate. Her blood glucose response to intravenous insulin was normal. The muscular weakness and hypotension might also be a result of the lack of 17-hydroxycorticosterone. The presence of hyperpigmentation is thought to be caused by an increased secretion of melanocyte-stimulating hormone, which is increased along with corticotropin in response to abnormally low levels of blood corticoid.[18] The presence of a positive water test may also suggest corticoid deficiency, whereas the normal electrolyte factor (Factor A) suggests normal aldosterone activity. This dichotomy has recently been studied by MacLean et al.[33] in hypophysectomized human beings. Corticoid administration in physiological dosage caused fading of the pigmentation and a normal water-load diuresis response in the patient under discussion. The response of the blood corticoids to corticotropin only while she was receiving intramuscular cortisone is not easily explained. It is possible that the corticotropin mobilized cortisone from the intramuscularly administered depot. This point is being further investigated in other Addisonian patients.

(*c*) *Androgen.*—Androgen production cannot be measured adequately during childhood because none of the secondary sexual characteristics are present and the urinary 17-ketosteroids are too low to measure accurately. The younger child failed to increase 17-ketosteroid output when given corticotropin.

The disease picture in these two patients can be differentiated from classical hypopituitarism with secondary hypoadrenalism. In both children there was excess growth, and in the younger the serum protein-bound iodine was slightly elevated. Neither had any symptoms or signs suggesting secondary hypothyroidism, and the presence of the anterior pituitary was demonstrated in the older girl. Associated hypoparathyroidism and moniliasis may develop subsequently, but to date there are no signs of these disorders. The adrenogenital syndrome with sodium deficiency has been excluded by repeatedly normal urinary 17-ketosteroids and the absence of virilization, as well as by the finding of adrenal atrophy in Patient 1. The preservation of aldosterone activity with absence of corticoid activity is the usual finding in hypopituitarism [31-33] and

has been observed in rats by Sanger and Stack-Dunn.[15]

Significance of the Pituitary Findings.—The chief histological findings in the pituitary gland of Patient 1 were marked decrease of both basophil and acidophil cells, with diffuse hyperplasia of small amphophil cells. There was no evidence of any hypothalamic damage, either on direct examination in Patient 1 or on clinical grounds in Patient 2.

Current evidence suggests that acidophils produce growth hormone and prolactin and that basophil cells produce the remaining pituitary trophic hormones. Gigantism is usually associated with acidophil hyperplasia, and Cushing's disease is at times associated with basophil adenomas. Purves and Griesbach[19] have elaborated evidence that basophil cells produce follicle-stimulating hormone, luteinizing hormone, and thyrotropic hormone, and Marshall[20] has shown that fluorescein-labeled antibody to corticotropin differentially stains the basophil cells of hog pituitaries. The experimental work of D'Angelo et al.[21] with starved guinea pigs also supports the hypothesis that corticotropin is manufactured by the basophils. Basophil cells have been reported to be degranulated in man when corticotropin or cortisone is administered.[25] However, Heinbecker and Rolf[22] working with dogs; Finerty and Briseno-Castrejon,[23] with rats; Herlant,[24] with sheep, and Russfield, Reiner, and Klaus,[34] with humans have reported evidence that acidophil cells elaborate corticotropin. Angevine[26] and Mosier[27] have observed in anencephalic infants and in newborn infants with hypoadrenalcorticism that there is a decrease in pituitary acidophils, although in anencephaly the decrease in basophils is more striking than the decrease in acidophils.

The histologic findings in the pituitary of Patient 1 are to a marked degree those most typically seen in human Addison's disease, i. e., decreased numbers of well-granulated basophils and of acidophils with an increased number of amphophil cells. Crooke and Russell[28] have reported detailed findings of the pituitary glands of patients dying of Addison's disease.

The pituitary of the patient who died appeared to be responding to the state of adrenal insufficiency, suggesting that the initial endocrine defect lay in the adrenal glands rather than in the hypophysis, a conclusion supported by the observation that the patient's adrenals showed much more marked atrophy of the zonae fasciculata and reticularis than is seen in children with protracted hypopituitarism. If this interpretation is correct, the patients can be considered to have primary, or "cytotoxic," adrenal atrophy with reactive pituitary change. Whether the adrenal atrophy is the result of common possession of a genetically determined metabolic defect in the adrenal cells or of common exposure to an infectious or toxic agent cannot be stated.

An alternative explanation is that the patients reported share a familial defect in anterior pituitary function which results in an inability to synthesize or secrete effective corticotropin. As has been mentioned, the amphophil hyperplasia of the pituitary of the patient who died presumably indicates that the gland was able to recognize the state of adrenal insufficiency and to attempt to respond to it, but whether corticotropin was actually secreted in increased amounts by either patient is not known. In the absence of evidence for a comparable selective defect concerning any other anterior pituitary hormone (i. e., inability of appropriate cells to secrete a hormone, rather than lack of the secretory cells), no opinion can be given as to whether amphophil hyperplasia of the type observed should occur in such a physiologic situation. A strain of mice with hereditary decrease in pituitary acidophils and resulting panhypopituitarism has been reported by Smith and MacDowell.[30]

Current usage applies the term amphophil[29,35,36] to actively secreting anterior pituitary cells, whether derived from basophil or from acidophil cells. By the histo-

logic methods employed by most workers, the ancestral cell type from which specific amphophil cells are derived cannot be determined with certainty. Presumably the majority of amphophils in the pituitary of the patient described are modified basophils either secreting or attempting to secrete corticotropin. Whether growth hormone and intermedin are secreted by the same cells is not known. The regular occurrence of hyperpigmentation in Addison's disease suggests that corticotropin and intermedin are made by the same pituitary cells and are oversecreted together when the adrenal target organ is destroyed. However, it seems equally possible that adrenal damage directly or indirectly leads to enhanced activity of two different pituitary cell populations which become indistinguishable amphophils. Similar considerations apply to growth hormone, evidence for oversecretion of which is found in a good many Addisonian patients, if food intake is maintained. In both patients reported, the evidence for enhanced secretion of growth hormone is the large body size. The reduction of the number of acidophil cells regularly found in the pituitaries of Addisonian patients suggests that acidophils as well as basophils are converted to amphophils, but whether such altered acidophils are actually secreting growth hormone, intermedin, corticotropin, or other hormones cannot be stated.

Summary

Two sisters with hyperpigmentation, weakness, and convulsions are described. One was studied by postmortem examination, and one was studied clinically. Their clinical findings appear to result from the absence of corticoid production. Evidence is presented that, although their corticoid production was inadequate, aldosterone production was normal. Selective damage of the zonae fasciculata and reticularis of the adrenal glands, perhaps due to genetically determined metabolic disorder or to common exposure to an infectious or toxic agent, can explain the findings reported, as possibly also can the specific inabilty of anterior pituitary basophil cells to secrete corticotropin (ACTH).

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Mechanisms of the Immediate Allergic Reaction and Some Therapeutic Implications

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Allergic disease in children is still thought of by many pediatricians solely from a clinical standpoint. Therapy under such circumstances remains empiric. Present knowledge of the mechanisms of the immediate allergic reaction is admittedly imperfect. Sufficient has been learned, however, to give what seems to be a rational explanation of the reaction and so to give a logical basis for certain forms of treatment.

Diagrammatic presentation usually makes a chain of events more easily understood. The schematic representation to be given here is a compilation of several which have been published previously together with some information not previously diagrammed.[1-3] It is in accord with and extends the concept of Boyd.[4a] One should not view this diagram, however, as the complete and final explanation of the immediate allergic mechanism but rather, as MacKay[5] pointed out a few years ago, as a template which we construct and then hold up against the real thing in order that the discrepancies between the two may yield fresh information. Such a diagram or model "subtracts out" what we think we understand, so that what is not yet understood is revealed more clearly.

Present understanding of allergic mechanisms is the result of studies in the disciplines of immunology, bacteriology, physiology, and pharmacology. To these studies must be added experiences in clinical medicine.

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Immunologic mechanisms seem to have been devised for the protection of man and animals from harmful contacts in their environment. Dienes[6] stated some years ago that antibodies in hay fever patients and those in patients infested with worms are similar. Boyd[4b] quotes Dienes to the effect that perhaps atopy is just an exaggerated response of the type which was originally protective against metazoan parasites. Boyd has expressed the view that reagin-type antibodies in parasitic infections need further study, and may be found to be of importance in resistance. Originally designed homeostatic mechanisms may become unhomeostatic or we may say that instead of homeostasis ("the wisdom of the body")[7] we sometimes must deal with hyperexis, meaning "having too much" or interpreted to mean "the stupidity of the body."[8]

Animals differ among themselves as to the ease of production of anaphylactic reactions and also as to the site of the reaction. Man differs from the lower animals. Care must be exercised, therefore, in directly applying the results of animal experiments to man. Experimental anaphylaxis and human atopic disease also are not identical.

In the study of hypersensitivity reactions we must be concerned not only with an antigen-antibody reaction but also with the tissues and the cells in or near which the reaction takes place. We must be concerned with reactions within the cells and with enzyme reactions. We must be concerned with the kind of antigens that will cause allergic disease. Brown[9] has very properly pointed out that we must be concerned about the harmfulness of "harmless" things.

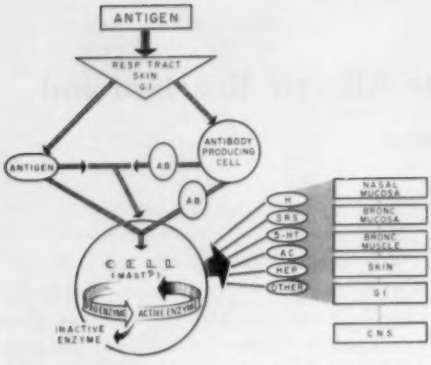

Fig. 1.—Mechanism of the immediate allergic reaction.

Figure 1 presents the mechanism of the immediate allergic reaction as presently conceived.

Entrance of Antigen Into Body

The first stage is the entrance of some antigen into the body. The antigen must be "complete" or else it must be a haptene that is either combined with protein or able to combine with tissue proteins to form a complete antigen.[4a] The common sites of entrance are the respiratory tract, skin, and gastrointestinal tract. It is also probable that certain antigens may cross the placental barrier to the fetus from the mother.[10]

Antibody Production

However, in the immediate type of reaction the site of the initial entrance of the antigen may make little difference. Initially some of the antigen gets to an antibody-producing cell either directly or after being acted upon by a macrophage. A specific cell type is not named in the diagram. However, it is well recognized that certain lymphoid cells are the antibody-producing cells. Those known to produce antibody are (1) the plasma cell without Russell bodies (Marschalko type); (2) the plasma cells with Russell bodies, and (3) the lymphoid cell in the germinal centers of lymphatic nodules.[11] Some workers have implicated only the plasma cell,[12-14] whereas others have implicated only the lymphoid cell.[15-17]

As recently as 1953 McMaster[18] cautioned investigators about accepting the evidence to that time as favoring either the plasma cell or the lymphocyte. At present the suggestion of Ortega and Mellors[11] seems reasonable—that each of the three morphologically distinct categories of cells that synthesize γ-globulin (antibody) represents a response to a particular form of antigenic stimulation.

In human allergic disease we are concerned with an antibody that differs in some respects from most, if not all, others. There is even some question whether reagin (skin-sensitizing antibody, reaginic antibody) is a real antibody.[19] Efforts to settle this point by protein electrophoresis have yielded conflicting evidence. "γ-Globulin" and "antibody" can probably be used as synonymous terms, as all of the usual antibodies have been shown to be γ-globulin and it is probable that all γ-globulin is antibody.[11]

Studies of serum from allergic persons have been carried out with the Tiselius apparatus, the starch-block apparatus, and the electrophoresis-convection apparatus. Results indicate that skin-sensitizing antibody may be in the α_2, β or γ-globulin fractions.[20-23] The line drawn between β-globulin and γ-globulin is often arbitrary, and these fractions may overlap.[21] Present evidence suggests that reagin is a β-globulin. On the other hand, the so-called blocking antibody, produced by hyposensitization procedures, is definitely a γ-globulin. Both reagin and blocking antibody are distinct physical entities.[21,24] Reagin, because of its difference from the more conventionally recognized antibodies, may not be produced by the same cells as the other antibodies. On the other hand, certain host differences may allow the usual antibody-producing cells to produce reagin.

The mechanism of antibody production in the cell is still uncertain. Three theories are currently extant: (1) the template theory of Haurowitz,[25] Alexander,[26] and Mudd,[27] modified by Pauling[28]; (2) the adaptive-enzyme or self-marker concept of

Burnet,[29] and (3) the natural-selection theory of Jerne.[30] Whether the skin-sensitizing antibody is produced by a variation of one of these mechanisms is still unknown. The time needed for sensitization to develop after introduction of the antigen is about 10 days, sometimes less. The antibody (reagin) produced may be demonstrated in the blood stream and also in the skin. Antibodies in the blood stream may be demonstrated by the passive transfer test (Prausnitz-Küstner reaction) and those in the skin by the scratch or intradermal skin test. If blood from a sensitized person is transfused to a nonsensitized person, reagin may be demonstrated in the recipient's blood for only a short time but may be demonstrated in the skin cells for several weeks.[19]

Which cells in the skin become sensitized is not known. It is tempting to think that the mast cells not only in the skin but elsewhere are the cells affected. Other cells, of course, may be involved also. Dale[31] has considered the smooth-muscle cells of the bronchioles to be sensitized.

Antigen-Antibody Reaction

When antigen is next introduced into the circulation it is met by antibody. There is some uncertainty whether union of the two takes place in the blood stream or in or on the sensitized cell. Perhaps union occurs in both places; at least there is experimental evidence to support this view.

As long ago as 1909 Friedberger[32] and Friedemann[33] found independently that if antibody and antigen were combined a precipitate formed. (They were not working with reagin.) This precipitate, if incubated with normal serum, yielded a toxic principle. Bordet[34] in 1913 found that a similar toxic principle could be produced by incubating agar or starch or some other polysaccharide with normal serum. This toxic principle was given the name "anaphylatoxin."

From 1913 to 1920 the work of Dale[35] and his group produced evidence of direct cellular reaction. He and Schultz independently showed that the contact of antigen with sensitized tissues caused reaction even in the absence of blood or serum. According to Dale,[36] histamine or a histamine-like substance is released by the reaction of antigen and sensitized cell, as was demonstrated by Manwaring, by Gebauer-Fuelnegg and associates, by Bartosch and associates, and by Dale. The anaphylatoxin concept was virtually abandoned during the period 1922 to 1940. Then Rocha e Silva[37] revived interest in anaphylatoxin and was able to demonstrate that it released histamine in the guinea pig.

Thus, two presumably different mechanisms were found to exert their action through a final common pathway: histamine release. It seems best at present to accept the probability of a dual mechanism rather than to insist on one or the other.

Next to be considered is the sensitized cell or cells. Such cells should contain the various chemical compounds that are released by the antigen-antibody reaction. The mast cell contains or makes many of these.[38] Its circulating analogue, the basophil, probably contains most of the blood histamine in man.[39,40] Evidence of which other tissue cells may be involved is lacking. One or more of the circulating blood cells may be involved as well.

Histamine and serotonin (5-hydroxytryptamine) have been found in platelets.[41,42] The work of Katz[43] demonstrated release of histamine from the sensitized blood cells (chiefly leukocytes, but also erythrocytes) of dogs, guinea pigs, and rabbits in vitro. Noah and Brand[44] found histamine release in vitro from blood cells from ragweed-sensitized persons. The most important blood cell concerned with the in vivo release of histamine or other mediators in man is still uncertain.

The mast cell is so important and so little has been written about it in the pediatric literature that something should be said about it here. According to Michels,[45] it was first named by Ehlrich in 1879 and was originally considered an overnourished connective-tissue cell. Hence, the name from

the German meaning "feeding." He first noted cells of this type at sites of chronic inflammation. They were considered of little practical importance until the study of their cytochemistry was begun [46] about 1935. Staemmler,[47] however, in 1921 had called attention to the possibility of their being unicellular "glands" of connective tissue for the production of mucin. Jorpes [48] found in studies between 1935 and 1946 that mast cells contain heparin. During that period and into 1950 evidence was accumulating that these cells could also release hyaluronic acid. It was not until 1953, however, that Riley [49] demonstrated that mast cells probably contain histamine. Subsequent work by him, West, and others has amply confirmed this.[38] Most recently serotonin (5-hydroxytryptamine) has been isolated from mast cells.[50] West,[38,51] however, has presented evidence that mast cells may not be as important releasers of 5-hydroxytryptamine as was originally thought. It is not known whether they contain or can make slow-reacting substance or acetylcholine.

A mechanism by which histamine may be released from the cell has been formulated recently by Mongar and Schild.[3,52] This is noted in Figure 1 by the ribboned lettering. In their articles these authors present evidence for an enzyme precursor (proenzyme) in the cell which is inactivated quickly under normal circumstances when it becomes active. Under other circumstances (at the time of antigen-antibody-proenzyme union), the active enzyme remains active and releases histamine. It should be stated, however, that some evidence in the past has been against the acceptance of enzyme release.[53] The work of Mongar and Schild demonstrated that release of histamine by the antigen-antibody reaction differs from that by chemical releasers such as 48/80 and octylamine. The former takes place only in the intact cell, and anoxia retards it. The drugs release histamine from either the intact cell or the cell particles, and anoxia accelerates the release.

Substances Released by Antigen-Antibody Reaction

Evidence now exists that histamine,[52,54] heparin,[55] 5-hydroxytryptamine,[56] acetylcholine,[57,58] a slow-reacting substance,[59] and perhaps others may be released by the antigen-antibody reaction. Some of the actions of these compounds are listed in the Table. Their action is primarily on blood vessels and smooth muscle. Further study may reveal that some of these substances produce their action by effecting the release of one of the others or by inhibiting the destroying enzyme of another.[42,56] Likewise, one may be more important in one species than in another. This concept of a release of several substances would be compatible with Dale's [31] concept of the origin of the threefold response, namely, that the response is attributable "probably not [to] histamine itself, but rather to an 'H-complex' . . . in the sense of a mixture of histamine itself with other natural . . . vasodilator substances, all readily released from the cell-protoplasm . . . and producing a combined reaction in which, however, the effects of the intensely active histamine would clearly predominate."

Some Actions of Substances Released by Antigen-Antibody Reaction

Substance	Dilates Small Vessels	Constricts Bronchi	Decreases Coagulability of Blood
Histamine	+	+	0
Heparin	0	0	+
Serotonin	Constricts	+	0
Acetylcholine (?)	+	+	0
Slow-reacting substance	0	+	0

The galaxy of released substances (chemical mediators) listed in the Table is an interesting group of compounds, and each substance merits a brief discussion.

Histamine is widely distributed in the body. The quantity varies from one organ to another. An organ such as the liver, which is rich in histamine in one species, such as the rabbit, may have very little

histamine in another, such as the guinea pig.[60] The histamine content of tissue parallels that of the mast cell.[61] Most workers feel that histamine plays an important but not exclusive role in the causation of allergic disease. The histamine-destroying enzyme has been called "histaminase," though some feel that it is more nearly correct to designate the enzyme "diamine oxidase."

One of the early criticisms of the histamine release theory was that this could not explain the increased coagulability of the blood in anaphylactic shock. In 1941 Jaques and Waters[55] found that heparin was released. The simultaneous release of histamine and heparin was demonstrated subsequently.[62] The former series of studies included one showing that the mast cells of the canine liver were reduced in number after anaphylactic shock. The presence of heparin in mast cells has already been mentioned. It also occurs in muscle. A heparinase has been described, though most of the heparin is excreted by the kidney either in depolymerized or active form.[48,63a]

5-Hydroxytryptamine (serotonin) is present in the gastrointestinal tract, blood platelets, spleen, brain, and lungs.[42,50] The content in the lung varies in different animal species. Although serotonin has been found in mast cells, West[51] has pointed out that high values for this substance and histamine do not occur in the same tissue. One substance seems to be able to be released without release of the other. There is some evidence that serotonin can act as a histamine releaser.[42]

Reserpine releases serotonin, while lysergic acid diethylamide and 2-bromo-lysergic acid diethylamide (Bol. 148) antagonize it.[64] The last two drugs are not suitable for use in man. In anaphylactic shock in the mouse, antihistaminic drugs are of little value, whereas lysergic acid diethylamide gives protection.[56] Monamine oxidase is the enzyme responsible for deactivation of 5-hydroxytryptamine.

The role of *acetylcholine* in allergic reactions is still uncertain. Its known physiologic and pharmacologic effects led a number of workers to consider it important. Two studies[57,65] supported this. However, two others[66,67] in the experimental field seemed to refute this. Peters and Silverman[68] in 1946, in a clinical study of a patient, obtained evidence that both histamine and acetylcholine were necessary to cause urticaria. Urbach and Gottlieb[69] in the same year suggested that several biologically active substances are concerned in the allergic reaction. Nakamura[58] has said that his experimental evidence supports the view that acetylcholine is far more important in mediating the anaphylactic reaction than is histamine.

Acetylcholine is found chiefly at nerve endings, where it mediates parasympathetic stimulation. It has been suggested that this substance acts by releasing histamine. It has also been suggested that emotionally induced asthma or hives is produced by this chain of events. Acetylcholine is inactivated by the enzyme "cholinesterase."

Slow-reacting substance is a compound of unknown chemical composition which is now believed to cause some of the bronchial obstruction in patients having asthma.[59] The first studies were carried out in Australia by Kellaway and Trethewie.[70] Then little about it was published until the last six years. Antihistamine drugs do not counteract its action. Experimental evidence suggests that the activity of slow-reacting substance A develops as a result of the union of antigen with fixed antibody in the cell. Slow-reacting substance A seems to potentiate the action of histamine by reducing the threshold of the histamine response and seems to be more active in man than in experimental animals. It is a difficult substance with which to work. The enzyme responsible for its inactivation is not known.

Hyaluronic acid is one of the best known of the extracellular substances of connective tissues. Its role, if any, in the allergic

reaction is not known. Its presence in the mast cell, however, cannot be ignored.

These chemical mediators, together perhaps with others yet unknown, play parts in the final assault on the blood vessels and the smooth muscle in the shock organs, and thus produce clinically recognizable allergic disease. This review of their functions of course has been slanted toward their function in this type of reaction. They also have roles to play in other conditions, both "normal" and stressful. Each substance is inactivated, as noted, by an enzyme which is usually found in close proximity to sites of release.

Mention has been made of the variation in response to the anaphylactic reaction in different species and the resistance of the intact rat and mouse to this type of shock. Hence great care must be exercised in transferring data obtained from anaphylactic study of animals to atopic study of man. It is possible, if not probable, that certain of the chemical mediators are more important in one species than another.[71]

Variations in Clinical Manifestations of Allergic Reactions

From a diagnostic and therapeutic standpoint we are interested in certain regions of the body, involvement of which causes the clinical syndromes of vasomotor rhinitis, asthma and hives, and some gastrointestinal manifestations of allergy. These regions are therefore mentioned in the diagram. The nervous system is mentioned chiefly because allergic disease often causes worry and concern on the part of the parent and patient and because the chronicity of these diseases often makes the patient irritable. The etiologic role of nervous and emotional factors cannot be disregarded, however.[72] This role may be mediated by acetylcholine, as has been indicated already. A primary allergic tension-fatigue syndrome has been described as well,[73] but there is no universal agreement as to its frequency of occurrence. Some instances of migraine, epilepsy, meningeal reactions, cranial and peripheral neuritis may have an allergic etiology.[73a]

The reasons for the occurrence of asthma in one child and hives in another when presumably the same preceding mechanism has taken place in each is not known. It may be due to a variation in end-organ response. Feldberg and Kellaway [74] pointed out that histamine acts locally at the site of liberation and that the symptoms produced may be different from those produced by the injection of histamine into the blood stream. Dale [75] subsequently suggested the "intrinsic liberation" of histamine, that is, liberation at the site of action, and also its "extrinsic liberation," that is, liberation at a site different from its point of action. One might wonder, then, whether the site of reaction in the child has an overabundance of mast cells.

When the present knowledge of the immediate allergic reaction is diagrammed one sees the many places where a defect in normal function could lead to abnormal organic behavior. In this it is not unlike the hemophilic group of diseases, the clinical pictures of which are similar, but the inherited coagulation defects of which are different. It may explain why patients vary in clinical manifestation and in response to treatment. Variations in dose of antigen, production of antibody, site of entrance of antigen, type of intracellular enzyme defect, release of chemical substances, activity and availability of their destroying enzymes, and end-organ response all may occur but in various combinations.

Therapeutic Aspects

Children having allergic disease must be cared for with presently available and commonly used forms of treatment. The advantages and limitations of each can be demonstrated best by reference to Figure 2.

Iodides, whether potassium or sodium, have only one action: to thin secretion in the respiratory tract. The dose must be adequate to produce an effect. Since thick bronchial secretions are found so frequently in children with asthma or asthmatic bronchitis and since all children who die of

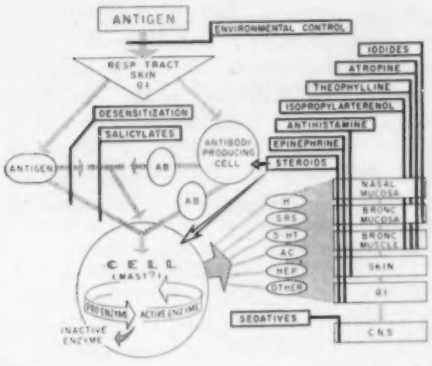

Fig. 2.—Representation of the role played by the various forms of treatment used in allergic disease.

asthma have many bronchi and bronchioles plugged with thick secretions, it is essential that some expectorant be used in treatment. My colleagues and I have found iodides best by far. Other expectorant drugs such as guaiacol guaiacolate and ammonium chloride are not nearly as effective. Moist air and an adequate intake of fluid are also important expectorant measures.

Atropine theoretically should be a good drug in the treatment of asthma. By parasympathetic blocking it produces a bronchodilating action. It or a related drug has been widely used in "asthmatic mixtures." The undesirable drying effect of such a drug on bronchial secretion, however, makes it unsuitable for use in the treatment of asthma in children. It may be of value in conjunction with epinephrine in the treatment of urticaria, as noted by Peters and Silverman.[68] Glaser [76] employs the drug in the treatment of hay fever.

The theophylline group of drugs (theophylline and theophylline ethylenediamine are the ones chiefly used in clinical practice) exert a direct dilating action on bronchial muscle. There is no apparent effect on bronchial or nasal mucosa, though Halpern [77] has credited them with promoting secretion from the bronchial glands because they are vasodilators.

Isopropylarterenol (Aludrine, Isuprel, Isonorin, Norisodrine) is used chiefly for its bronchodilating effect. This is seemingly due to its sympathomimetic action. It is considered at present to be the strongest of the bronchodilating agents. For this reason it is commonly used as the bronchodilating drug when pulmonary function is studied. It is also said to have some expectorant action.[78]

The antihistamine group of drugs is a chemically heterogeneous group which has many actions in addition to the one of competing with histamine for the sites which histamine usually selects for action. It is now well recognized that these drugs do not in any way affect the antigen-antibody reaction or the mechanism by which histamine is released. The drugs must be given in adequate dosage and usually early in the course of the allergic reaction to exert their best effect. They are of no value at all in counteracting the effects of slow-reacting substance, 5-hydroxytryptamine, or heparin. Some seem to have an anticholinergic action.[79] It was early thought that diphenhydramine (Benadryl) and tripelennamine (Pyribenzamine) might have some bronchodilating effect. Recent evidence,[80] however, indicates that many of these drugs have a bronchoconstrictive action and may under some circumstances serve as chemical releasers of histamine.

These drugs effectively compete against histamine in the mucosa of the respiratory tract and in the skin. They seem to have no effect against the action of histamine in the gastric secretion.

Epinephrine has been and still is the best drug with which to treat the acute, severe, immediate allergic reaction. Its sympathetic stimulating action is prompt and affects all the tissues involved. It has both a bronchodilating action and an antiedema action because of its vasoconstricting effect.

Ephedrine and the various drugs related to it (Propadrine, pseudoephedrine) have similar actions. They, however, are used orally for the most part and have a slower but more prolonged action than epinephrine.

There is some evidence that ephedrine acts by suppressing monamine oxidase which destroys epinephrine.[62b]

Steroids (corticotropin [ACTH], cortisone, hydrocortisone, and the delta analogues, that is, the glucocorticoid compounds used in clinical practice at the present time) seem to have a threefold effect on the allergic reaction; undoubtedly there are other kinds of actions that are not now recognized.

1. The antiphlogistic effect is the anti-inflammatory action by which the capillaries are made less permeable.[81] This action is at the site of the inflammatory response and is not the result of systemic mechanisms. The greater the inflammation, the larger the dose of steroid necessary to combat it.

2. The effect on antibody production is poorly understood. Dixon's work[82] indicates that the steroids must be given either before or a few hours after the sensitizing antigen is given if they are to interfere with the production of antibody. Dews and Code[83] showed that in the rat adrenalectomy enhanced anaphylaxis, though not by increasing antibody content of the blood. Yet the administration of cortisone to adrenalectomized rats during sensitization reduced the development of sensitivity. The administration of cortisone, however, to rabbits either intact or adrenalectomized lowered greatly the resulting concentration of circulating antibody and inhibited the development of cutaneous sensitivity. McMaster and Edwards[84] have shown that antibody-producing organs, while under the influence of cortisone, will take up antigen but will not produce antibody. On cessation of administration of the steroid, the production of antibody begins. Very large doses of corticotropin or cortisone are required to suppress circulating antibody,[81] and even when the antibodies are almost suppressed, anaphylactic shock can still occur. Antibody-suppressive doses in man to correspond with those used in experimental animals are far beyond the doses usually given in clinical medicine.

3. The steroids affect the metabolism of histamine. Schayer[85] and Halpern[86] have shown that cortisone interferes with the biogenesis of histamine in the rat. Skin cells depleted of histamine regain it very slowly when the animal is receiving cortisone. Skin cells of adrenalectomized rats receiving no cortisone regain histamine rapidly.

Holman and Goth[87] reported that in man cortisone did not prevent histamine release by a single injection of a histamine-releasing drug but did make the site less responsive to subsequent injections, thus suggesting that human skin may behave like rat skin.

In studies of both adults and children, as judged by urinary studies of histamine,[88] the excretion of free histamine tended to be decreased during acute allergic episodes. When steroids were given therapeutically, elimination of free histamine in the urine increased coincidental with the remission of clinical symptoms.

The favorable effect of the steroids is usually not clinically evident for 12 to 24 hours. The increase in free histamine in the urine is not evident for 24 to 36 hours. There is a slight increase in the urinary free histamine in normal persons during the administration of the steroids.[89]

Clinical experience has demonstrated the value of the steroids in the treatment of allergic disease. Much more work remains to be done to explain completely just why they are of value.

Sedatives, particularly barbiturates and chloral hydrate, are frequently employed either alone or in combination with some of the aforementioned drugs in the treatment of children suffering from allergic disease. They have no direct effect on organs concerned in the allergic reaction. The so-called tranquilizer drugs have been used in the treatment of some children who have chronic or frequently recurrent asthma. It is uncertain whether they do more than help to relax the patient. Chlorpromazine is very closely related chemically to promethazine

(Phenergan), one of the antihistaminic drugs.

Salicylates have been used off and on for years in the treatment of allergic disease. While some of the therapeutic value may be due to their analgesic action, it is possible that there may be some interference with the antigen-antibody union. Some experimental work indicates that salicylates may interfere with antibody production and also with release of histamine and slow-reacting substance when sensitized tissue is exposed to antigens.[1]

Desensitization, perhaps better called "hyposensitization," seems to have its favorable effect as a result of the production of blocking antibodies by the treated child. These blocking or inhibiting antibodies were first described by Cooke and coworkers[90] in 1935. They seem to act by preventing union of reagin and antigen by uniting with the antigen. The work of Loveless and others[91] has added to the knowledge of these thermostable antibodies. It has been difficult to correlate the titers of blocking antibodies with the clinical course of the patient.[19] It is not known how an antibody in the blood can protect a sensitized cell apparently damaged directly by antigen, as in hay fever.

Environmental control is much discussed and often poorly understood and therefore frequently inadequately carried out. It is one of the most important therapeutic measures. The most obvious example is transporting a ragweed-sensitive child to a ragweed-free area during the pollen season. A dust-free (or, better stated, dust-poor) bedroom is essential in the treatment of patients who are sensitive to house dust. If such a room is properly prepared and meticulously maintained, it is very effective. Environmental control prevents the antigen from getting into the body of the clinically sensitive child, or at least permits only small amounts to enter the body. The chain of events known as the immediate allergic reaction is thereby obviated or minimized.

Summary

Current knowledge of the mechanism of the acute allergic reaction is diagrammed to aid in better understanding of what is known and what is not known of it. Present means of treating this reaction and its clinical manifestations are fitted into this diagram to demonstrate their usefulness and limitations.

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The Essential Amino Acid Requirements of Infants: Lysine

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Acurate knowledge of essential nutrients is a *sine qua non* of good nutrition. Such information is needed for the prevention and repair of dietary deficiencies arising from food shortages and also in situations where the capacity to handle food is limited by disease states. Evaluation of the requirements for essential amino acids has been peculiarly difficult, since this involves the construction of a diet in which the quantity of a single amino acid can be varied at will. The problem has been approached in several ways:

1. Use has been made of natural proteins deficient in one or another amino acid. This method has very limited applicability, for nature has been singularly unobliging in providing a variety of such proteins.

2. Chemically degraded proteins or protein hydrolysates have been used. A number of procedures can be used to destroy one or more amino acids, which can then be replaced in any quantity desired. Diets constructed from such preparations have the advantage that the amino acids are present for the most part as the natural isomers and that unessential as well as essential amino acids are present. There is, however, the disadvantage that the nature and possible effects of the degraded fragments are unknown.

3. Mixtures of pure amino acids can be used to provide the protein fraction of the diet. Such diets have the advantage that all the ingredients are accurately known, but they have the disadvantage that, because of expense certain amino acids have had to be supplied as DL-forms: The limited ability of the body to utilize the unnatural forms of the amino acids and the unknown effects of these unnatural isomers have introduced uncertainties in the studies. Furthermore, the fact that the nonessential amino acids have been for the most part omitted, necessitating their synthesis from other amino acids, likewise detracts from the value of the data.

4. A fourth method of approaching amino acid requirements is to calculate the intake on known diets compatible with health. This method gives only an outside figure: one can say only that the requirement must be less than the intake on such a diet.

The difficulties mentioned can be obviated by providing the nitrogen moiety of the diet as a mixture of pure amino acids, all in their natural L-forms, a mixture which provides the unessential as well as the essential amino acids, avoiding the necessity of synthesizing the latter. In recent years the natural isomers of all the amino acids have become available in quantities suitable for infant diets, and we have therefore used this approach in the present experiments designed to evaluate the lysine requirement of the infant, as we had previously done in the case of threonine [1] and phenylalanine.[2]

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TABLE 1.—*Composition of Experimental Diet*

	Gm.	% of Total Calories
L-Amino acid mixture *	100	12
L-Alanine	2.67	
L-Arginine	4.58	
L-Aspartic acid	8.78	
L-Cystine	2.14	
L-Glutamic acid	17.56	
L-Glycine	2.06	
L-Histidine	1.76	
L-Isoleucine	6.11	
L-Leucine	11.76	
L-Lysine hydrochloride	7.10	
L-Methionine	1.66	
L-Phenylalanine	4.80	
L-Proline	6.11	
L-Serine	5.34	
L-Threonine †	4.56	
L-Tyrosine	4.56	
L-Tryptophan	1.66	
L-Valine	6.64	
Hydrogenated vegetable fat ‡	160	43
Dextri-Maltose §	375	45
Mineral mixture ‖	22.3	
B vitamin mixture ¶		10.0 ml. per day
Vitamins A, C, and D supplied as TriVisol		0.6 ml. per day

* The amino acids were obtained from various commercial sources. They were checked for purity by column chromatography and specific rotation. In some instances further purification was necessary.

† Supplied by Winthrop Stearns, Inc.

‡ Crisco, supplied by Procter and Gamble.

§ Supplied by Mead Johnson and Co.

‖ The composition of the mineral mixture was as follows: NaCl 18.9%, $CaHPO_4$ (anhydrous) 25.4%, $MgSO_4$ (anhydrous) 6.8%, $KHCO_3$ 44.4%, KCl 2.88%, Fe₃ Citrate 2.21%, $CuSO_4$ (anhydrous) 0.24%, $MnSO_4$ (anhydrous) 0.15%, KI 0.015%, NaF 0.03%.

¶ The composition of the B vitamin mixture was as follows: thiamine 0.38, riboflavin 2.0, nicotinamide 0.85, calcium pantothenate 3.5, pyridoxine 0.67, hexahydroxycyclohexane 150, para-aminobenzoic acid 0.5, folic acid 0.05, choline chloride 147, biotin 0.03, cyanocobalamine 0.015 mg.

Methods

A synthetic diet was used, the nitrogen moiety of which was composed of a mixture of 18 L-amino acids. The procedure was to give the full diet as a control, then to remove the lysine completely from the mixture, and subsequently to reintroduce it in a stepwise fashion until normal growth was resumed. Nitrogen intake was kept constant by the substitution of glycine for the lysine. The criteria of normal growth included the weight gain, the nitrogen retention, and the level of serum protein. Quantitative determination of the urinary lysine excretion was also carried out with the thought that this might also act as a criterion of the adequacy of the lysine intake.

A word should be included here about our criteria of adequacy. We chose as adequate that intake of lysine which allowed weight gain and nitrogen retention to proceed at the same rate as they did during control periods at the beginning and end of the study. At times there was dissociation of these two functions, and weight gain was adequate on intakes of lysine that resulted in inadequate nitrogen retention. In these instances we chose as requirement the next higher intake of lysine which was also associated with normal nitrogen retention. We are also aware of the pitfalls involved in using "normal" nitrogen retention as a criteria of adequacy. The amount of nitrogen retained is a variable figure which tends to fluctuate even under the most constant conditions, since there are certain periods of growth during which more nitrogen is laid down. There are also certain babies who seem to retain more nitrogen than others. The nitrogen intake influences the retention; thus breast-fed infants always retain less nitrogen than those fed cow's milk. The quantity of nitrogen retained is also affected by age, being much higher during the first few months of life than it is during the latter part of the first year. For all these reasons, we allowed each baby to serve as his own control and did not attempt to compare our figures with those available in the literature. Nitrogen retention data are certainly not infallible: they are, however, the best laboratory test now available for studies of the type we are reporting.

Diet.—The diet used in this study supplied the 18 L-amino acids in the proportions found in breast milk, the figures used being those compiled by Macy et al.,[3] modified in a few instances by the data of Cheung et al.[4] Carbohydrate was provided in the form of Dextri-Maltose, and fat was added in the form of a hydrogenated vegetable fat. A vitamin mixture and a mineral mixture were also included in the diet. Details of the diet are given in Table 1.

Four of these infants were given 125 Cal. per kilogram of body weight daily. It was necessary to raise the caloric intake to 150 Cal. per kilogram to obtain satisfactory weight gain in the other two infants.

TABLE 2.—*Lysine Intake of Each Infant*

	Lysine Intake, Mg/Kg/Day	
Baby	Inadequate	Adequate
A	88	103
B	89	102
C	74	88.4
D	74.5	88.5
E	73.5	90.5
F	--	87.5

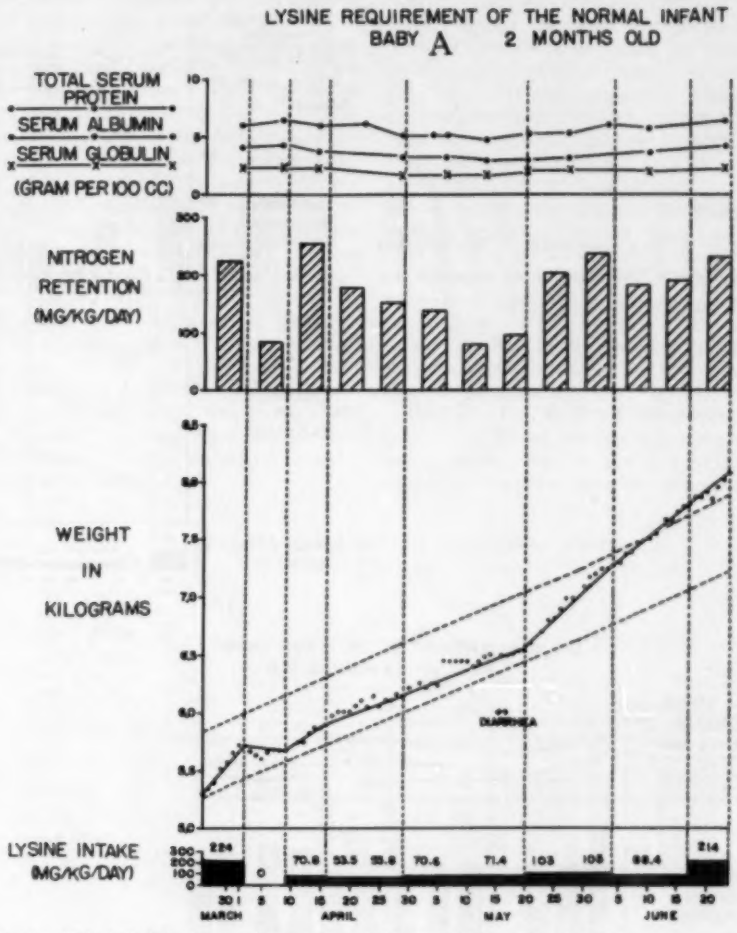

Fig. 1.—This baby's lysine requirement was 103 mg/kg/day. The dotted lines represent the 75th and 90th percentile curves.

Metabolic Data.—These were obtained on all six of the infants included in this study. Complete collection of urine and stool over the four-day metabolic period was made possible by the use of special metabolic beds[6]; experienced metabolism nurses supervised these collections. When the diet was shifted, this was done three days before the beginning of a new metabolic period.

The 24-hour urine specimens were collected separately, preserved with thymol-chloroform, and frozen whenever the analyses could not be performed immediately. The stools for the four-day period were marked by carmine at the beginning and charcoal at the end of the period. They were kept in the frozen state until the nitrogen determination could be carried out.

Blood for serum protein determinations was performed within two hours.

Analytical Procedures.—Total nitrogen in urine and stool was determined by the Kjeldahl procedure recommended by Hiller et al.[8] Plasma proteins were determined by the arginine method.[7] Alpha amino nitrogen was determined by the gasometric ninhydrin-carbon dioxide method of Van Slyke et al.[9] The procedure of Bonsnes and Taussky[9] was used for determination of creatinine.

The urinary lysine excretion was measured by a modification of the ion exchange resin column technique of Moore and Stein.[10] The short column was used and only two buffers were introduced: pH 5.0±0.1 and pH 6.8±0.3. The second buffer was used after 22 to 25 fractions had been collected,

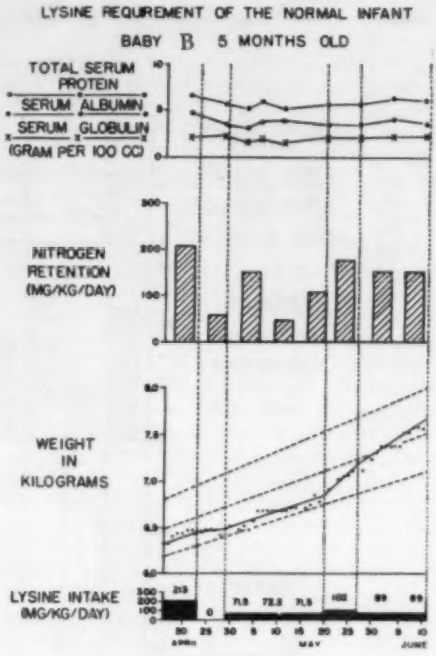

Fig. 2.—The lysine requirement of this baby was 102 mg/kg/day. The dotted lines represent the 10th, 25th, and 50th percentile curves.

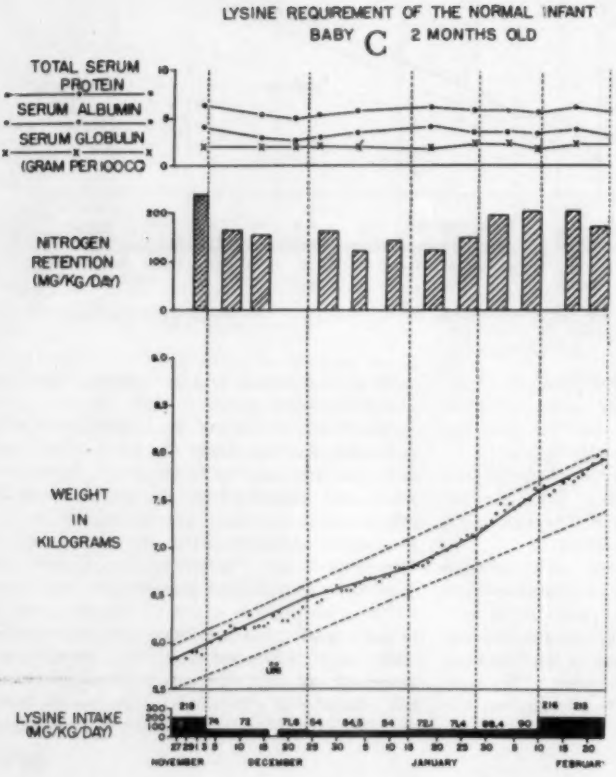

Fig. 3.—This baby had a lysine requirement of 88.4 mg/kg/day. The 75th and 90th percentile curves are indicated by the dotted lines.

and the analyses were then continued until approximately 150 fractions were collected.

Observations on the Lysine Requirement.—The lysine requirement was studied in six normal infants who remained in the hospital for social reasons. The intake of lysine required for normal growth was very similar in all six infants. Four of them met our criteria of normal growth when receiving 90 mg. per kilogram per day of the lysine while the remaining two needed 102 to 105 mg. per kilogram per day of lysine to gain well. A summary of the lysine intakes in these studies is presented in Table 2. The individual protocols follow.

BABY A.—This baby was born Jan. 29, 1955, weighing 3.9 kg. He remained in the hospital for social reasons. He was 2 months old and weighed 5.3 kg. when he became a subject in the study. This placed his weight between the 75th and 90th percentile for his age using the Harvard Growth Standards.[11] He had an attack of mild diarrhea during the study.

When lysine was completely removed from this infant's diet he lost weight and had poor nitrogen retention. An intake of 70 mg. per kilogram appeared satisfactory the first time it was tried; however, when this same amount of lysine was fed in three subsequent metabolic periods it failed to support normal weight gain and nitrogen retention. His weight gain on intakes of 103, 105, and 90 mg. per kilogram per day was excellent and equal to that on the full amino acid diet. However, nitrogen retention on 90 mg. per kilogram per day was not as good as it was on intakes of 103 and 105 mg. per kilogram per day. Hence, this infant's lysine requirement appears to be between 90 and 103 mg. per kilogram per day. His weight curve rose from between the 70th and the 90th percentile to a point above the 90th percentile during the period of adequate lysine intake.

BABY B.—This baby was born Nov. 9, 1954, birth weight 2.2 kg. He stayed in the hospital for social reasons, and he was 5 months old and weighed 6.3 kg. when the study was started. This

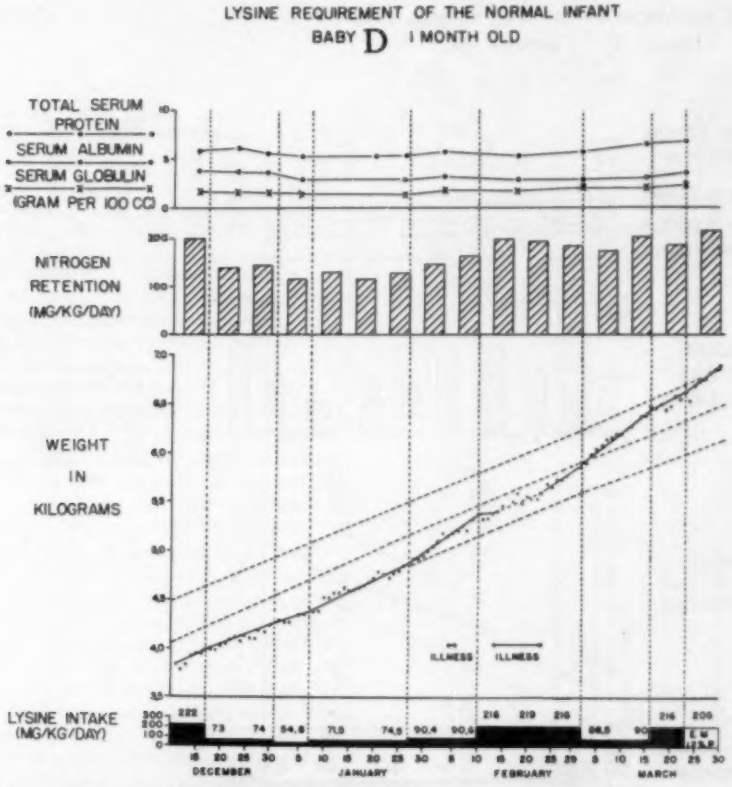

Fig. 4.—This infant's lysine requirement was 88.5 mg/kg/day. The dotted lines are the 10th, 25th, and 50th percentile curves.

weight was between the 10th and the 25th percentile. He did not suffer any intercurrent infection during the course of the study.

When lysine was omitted from the diet of this infant, he stopped gaining weight and had subnormal nitrogen retention. His growth performance was not satisfactory on 72 mg. per kilogram per day but was good on an intake of 102 mg. per kilogram per day. An intake of 89 mg. per kilogram per day showed less satisfactory results than the 102 mg. per kilogram per day, which was considered to be this child's lysine requirement. When he received adequate lysine, his weight curve rose from between the 10th and the 25th percentile curves to the next higher channel.

BABY C.—This child was born on Sept. 22, 1955, birth weight 2.75 kg. He remained in the hospital because his mother had active tuberculosis, but the child never had any contact with her. He was included in the study at 2 months of age, when he weighed 5.8 kg. This was between the 75th and the 90th percentile. He contracted one minor upper respiratory tract infection during the course of the study.

He did not gain weight well or retain normal amounts of nitrogen on intakes of 54 and 72 mg. per kilogram per day. When he received 90 mg. per kilogram per day, he gained as much weight and retained as much nitrogen as he did on full lysine intake. This baby maintained his weight between the 75th and 90th percentile curves during the entire study.

BABY D.—This baby was born Oct. 2, 1955, birth weight 2.75 kg. He remained in the hospital for social reasons and was 6 weeks of age and had attained a weight of 3.72 kg. when he was included in the study. This was between the 10th and the 25th percentile. During the course of this study, he developed an abscess on the jaw and otitis media, both of which responded promptly to antibiotic therapy. He continued to gain weight well during the time he had these infections. It is apparent from the accompanying figure (Fig. 4) that intakes of 54, 73, and 74 mg. per kilogram

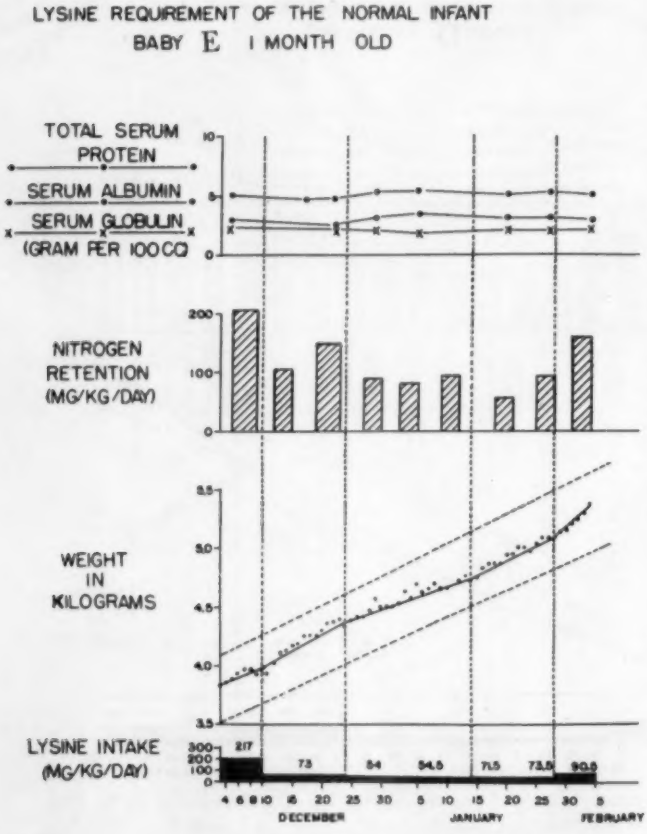

Fig. 5.—The lysine requirement of this baby was 90.5 mg/kg/day. The dotted lines represent the 10th and 50th percentile curves; this subject's weight curve lay just on the 25th percentile.

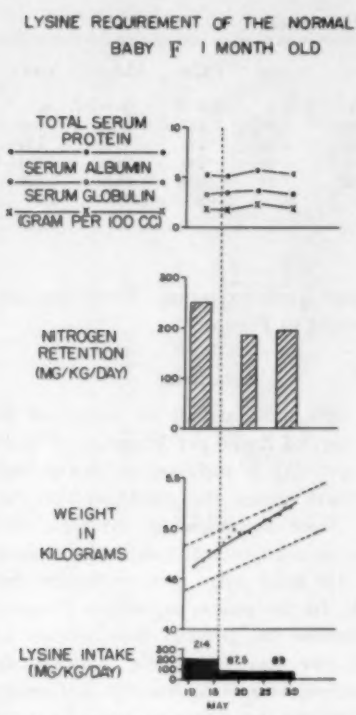

Fig. 6.—This infant had a lysine requirement of 87.5 mg/kg/day. The 50th and 75th percentile curves are shown by the dotted lines.

per day of lysine were not sufficient for normal growth in this baby. An intake of 90 mg. per kilogram per day on two separate occasions allowed good weight gain and nitrogen retention. Control periods of full amino acid intake and of an isonitrogenous evaporated milk formula carried out at the end of the study gave weight gains and nitrogen retentions similar to those on the 90 mg. per kilogram per day intake. This baby's weight, which was between the 10th and the 25th percentile at the onset of the study rose above the 25th percentile when 90 mg. per kilogram per day of lysine was given.

BABY E.—This baby was born Nov. 8, 1955, birth weight, 3.1 kg. He remained in the hospital because of social reasons, and he was one month old and weighed 3.75 kg. when he became a subject in the study. This weight was between the 10th and the 25th percentile. He remained well during the entire course of the study. Intakes of 54, 73, and 74 mg. per kilogram per day were not adequate in this subject. When he was given 90 mg. per kilogram per day, his weight gain was much improved and his nitrogen retention was better than it had been on the previous intakes of lysine, but not as good as it had been in the control period at the

TABLE 3.—*Baby A: Metabolic Observations*

Date	3/28-31	4/4-7	4/11-14	4/18-21	4/25-28	5/2-5	5/9-12	5/16-19 *	5/23-26	5/30-6/2	6/6-9	6/13-16	6/20-23
Lysine intake, mg/kg/day	224	0	70.8	53.5	53.8	70.0	71.4	71.4	103	108	88.4	89	214
Av. wt., kg.	5.55	5.65	5.81	6.03	6.12	6.26	6.45	6.53	6.83	7.19	7.47	7.72	7.94
Nitrogen intake, gm/day	2.58	2.71	2.71	2.86	2.91	2.91	3.09	3.09	3.09	3.39	3.48	3.61	3.72
Nitrogen in urine, gm/day	1.23	2.13	1.08	1.47	1.66	1.65	2.17	1.68	1.37	1.41	1.81	1.84	1.54
Nitrogen in stool, gm/day	0.12	0.10	0.15	0.31	0.32	0.39	0.39	0.78	0.29	0.31	0.29	0.32	0.31
Nitrogen retention, mg/kg/day	224	85	254	178	182	139	80	95	208	234	184	189	233
Urine Creatinine, mg/kg/day	13.0	13.6	13.7										
Urine amino nitrogen, mg/kg/day	4.87	6.01	5.73									1.61	
Lysine excretion, mg/kg/day †	3.35	0.50	1.3			1.02	0.75			1.78			

* Diarrhea during this period.
† This may include small amounts of 1-methyl histidine and ornithine.

TABLE 4.—*Baby B: Metabolic Observations*

Date	4/18-21	4/25-28	5/2-5	5/9-12	5/16-19	5/23-26	5/30-6/2	6/6-9
Lysine intake, mg/kg/day	213	0	71.5	72.2	71.5	102	89	89
Av. wt., kg.	6.44	6.45	6.52	6.69	6.78	7.07	7.34	7.57
Nitrogen intake, gm/day	3.0	3.08	3.08	3.20	3.20	3.20	3.45	3.54
Nitrogen in urine, gm/day	1.32	2.31	1.76	2.04	2.14	1.58	2.03	2.09
Nitrogen in stool, gm/day	0.25	0.41	0.35	0.24	0.34	0.35	0.29	0.29
Nitrogen retention, mg/kg/day	220	56	151	48	106	179	155	153

beginning of the study two months earlier. It was unfortunate that we were unable to carry out another period of full amino acid intake at the close of the study, since nitrogen retention tends to fall off with increasing age. His weight stayed between the 10th and 50th percentile curves for the duration of the study.

BABY F.—This baby was born April 5, 1954, weighing 3.2 kg. Active tuberculosis in his mother made it necessary for him to remain in the hospital, but he never had any contact with her. He was one month old and had attained a weight of 4.5 kg. when he was included in the study. This weight lay between the 50th and 75th percentile. It was possible to study this infant on only two different levels of lysine: the full amount and approximately 90 mg. per kilogram per day. He gained weight as well on intakes of 87 and 89 mg. per kilogram per day as he did on full lysine intake. The nitrogen retention was slightly less at the lower figure but was still in the same range as that encountered in normal babies receiving full diets. This intake of lysine permitted his weight curve to remain between the 50th and 75th percentile curves.

There were no consistent changes in the serum proteins during the periods of inadequate lysine intake. No clinical symptoms appeared in the two infants who received diets containing no lysine for a period of one week each.

Metabolic Observations.—The metabolic data obtained are summarized in Tables 3 to 8. During periods of lysine deficiency, excess nitrogen was excreted in the urine, presumably in the form of urea. Apart from this, there was no general trend that could be correlated with periods of inadequate lysine intake. The α-amino nitrogen excretion was little affected. Nitrogen absorption was not affected by lysine deficiency.

It was possible to determine the lysine excretion at various levels of intake in three of the subjects. These determinations revealed a definite parallelism between lysine intake and lysine excretion. These data are summarized in Figure 7.

Comment

Our data indicate that an intake of 90 to 105 mg. of lysine per kilogram of body weight per day is sufficient to permit normal growth under the conditions of this study. Since a completely synthetic diet was fed, it is important to ascertain if these figures are valid when a more natural diet is used. In the course of studies designed to determine the protein requirements of infancy, we have gradually reduced the milk content of an evaporated milk formula while keeping the nitrogen intake constant by the addition of unessential nitrogen in the form of urea or glycine. The caloric intake was also kept constant by the addition of fat and carbohydrate. Four infants who have been fed in this fashion have grown normally and maintained excellent health while receiving formulae which contained only 4% of the calories in the form of milk protein. Calculation of the lysine intake using figures for the lysine content of milk available in the literature[8] reveals that these infants were receiving on the average 84 mg. per kilogram per day. Infants fed breast milk also do well on lysine intake of similar magnitude. Fomon and May[12] fed carefully measured amounts of pooled breast milk to, and obtained nitrogen balances on, infants under 6 months of age. These infants received 2.4 gm. per kilogram of breast milk protein during the first 60 days of life and 1.6 gm. per kilogram thereafter. We have calculated that these infants received, respectively, 129 and

TABLE 5.—*Baby C: Metabolic Observations*

Date	11/28-12/2	12/5-8	12/12-15	12/26-29	1/2-5	1/9-12	1/16-19	1/22-25	1/30-2/2	2/6-9	2/13-16	2/20-23
Lysine intake, mg/kg/day	218	74	72	54	54.5	54	72.1	71.4	88.4	90	216	215
Av. wt., kg.	5.87	6.12	6.25	6.49	6.62	6.76	6.82	7.10	7.34	7.53	7.72	7.90
Nitrogen intake, gm/day	2.79	2.86	2.97	3.09	3.18	3.23	3.26	3.32	3.42	3.57	3.20	3.42
Nitrogen in urine, gm/day	1.02	1.52	1.75	1.84	2.23	2.10	2.22	2.13	1.83	1.89	1.53	1.93
Nitrogen in stool, gm/day	0.36	0.31	0.28	0.19	0.13	0.14	0.17	0.13	0.17	0.16	0.11	0.15
Nitrogen retention, mg/kg/day	239	167	151	163	123	146	127	149	192	201	201	170
Urine creatinine, mg/kg/day	13.4	14.8	14.7					17.9		18.4		16.6
Urine amino nitrogen, mg/kg/day	4.28	6.98	7.18					8.32		9.75		6.95
Lysine excretion, mg/kg/day	4.24	1.37	0.29					1.47		2.02		6.20

TABLE 6.—*Baby D: Metabolic Observations*

Date	12/12-15	12/19-22	12/26-29	1/2-5	1/9-12	1/16-19	1/22-25	1/30-2/2	2/6-9	2/13-16 *	2/20-23 *	2/27-3/1	3/5-8	3/12-15	3/19-22	3/26-29 (milk formula)
Lysine intake, mg/kg/day	222	73	74	54.8	71.5	71.5	74.5	90.4	90.6	216	219	216	88.5	90	216	205
Av. wt., kg.	3.86	4.05	4.15	4.30	4.50	4.64	4.76	5.02	5.25	5.43	5.55	5.80	6.10	6.26	6.51	6.78
Nitrogen intake, gm/day	1.88	1.98	2.02	2.07	2.13	2.20	2.34	2.38	2.54	2.40	2.64	2.76	2.85	2.97	3.11	3.18
Nitrogen in urine, gm/day	0.98	1.28	1.26	1.46	1.46	1.53	1.54	1.51	1.47	1.04	1.33	1.51	1.62	1.48	1.74	1.56
Nitrogen in stool, gm/day	0.11	0.12	0.15	0.10	0.09	0.13	0.19	0.15	0.22	0.28	0.23	0.18	0.18	0.19	0.18	0.17
Nitrogen retention, mg/kg/day	203	142	148	118	130	115	128	144	161	198	194	183	172	206	182	212

* Illness during these periods.

TABLE 7.—*Baby E: Metabolic Observations*

Date	12/5-8	12/12-15	12/19-22	12/27-29	1/2-5	1/9-12	1/16-19	1/23-26	1/30-2/1
Lysine intake, mg/kg/day	217	73	73	54	54.5	54.5	71.5	73.5	90.5
Av. wt., kg.	3.93	4.10	4.31	4.50	4.62	4.69	4.87	5.04	5.21
Nitrogen intake, gm/day	1.86	1.93	2.07	2.14	2.20	2.26	2.29	2.44	2.49
Nitrogen in urine, gm/day	0.95	1.32	1.26	1.40	1.64	1.69	1.86	1.83	1.55
Nitrogen in stool, gm/day	0.09	0.19	0.16	0.17	0.17	0.13	0.14	0.14	0.16
Nitrogen retention, mg/kg/day	208	103	150	127	84	94	59	93	149
Urine creatinine, mg/kg/day	10.5		9.65		12.8	12.5	12.0	11.7	11.3
Urine amino nitrogen, mg/kg/day	5.15		4.35		5.55	5.7	6.3	4.83	2.86
Lysine excretion, mg/kg/day	5.25		0.85		0.10	1.46	1.7	2.06	1.08

86 mg. per kilogram per day of lysine while gaining well and retaining adequate amounts of nitrogen. We do not know if they would also have done well on smaller intakes of lysine, since lower protein intakes were not tried in this study.

Our figures are considerably less than the 140 to 200 mg. per kilogram suggested by Albanese [13] to be the lysine requirement of the infant. Since the metabolic data which led to this conclusion have never been published, it is impossible for us to explain this discrepancy satisfactorily. However, it is possible that the wheat gluten used as the lysine-poor protein in his studies may have altered the lysine requirement. Amino acid imbalances are known to occur in this protein, and it is also possible that some damage to the protein occurred in the processing. Either of these factors may conceivably have raised the lysine requirement.

It is of interest that in our studies the serum proteins, as determined by the arginine method, were not increased during periods of deficient lysine intake, even during the two periods on zero lysine. This in contrast to the findings of Albanese,[14] who reported such increases on lysine-deficient diets based on wheat gluten when the arginine method was used.

Supplementation of milk formulae with lysine would seem to be totally unnecessary: the usual infant who is fed a cow's milk formula receives three times as much lysine as he requires for normal growth. Whether there exist pathological conditions in which additional lysine is beneficial remains to be demonstrated. The possibility of harm from the creation of amino imbalances by excesses of certain amino acids, including lysine, has been pointed out in various publications.[15,16]

TABLE 8.—*Baby F: Metabolic Observations*

Date	6/12-15	6/20-23	6/27-30
Lysine intake, mg/kg/day	214	87.5	89
Av. wt., kg.	4.67	4.96	5.17
Nitrogen intake, gm/day	2.17	2.30	2.46
Nitrogen in urine, gm/day	0.73	1.22	1.26
Nitrogen in stool, gm/day	0.22	0.16	0.20
Nitrogen retention, mg/kg/day	258	184	193

Summary

The lysine required by the normal infant was determined on a diet in which 18 L-amino acids served as the source of nitrogen. Four of these infants required 90

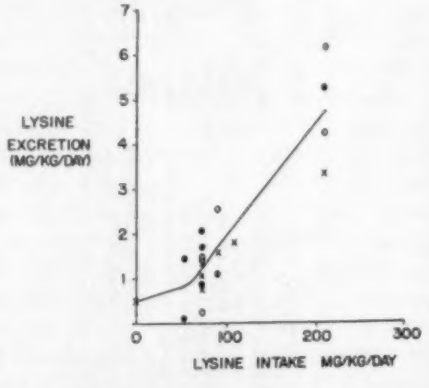

Fig. 7.—Relation of lysine excretion in urine to lysine intake. Solid circle, Baby E; open circle, Baby C; cross, Baby A.

mg. of lysine per kilogram per day, while two required 102 to 105 mg. per kilogram per day to grow normally. Criteria of normal growth included weight gain, nitrogen retention, and the maintenance of normal serum protein values. During the periods of deficiency, the weight gain was impaired and excess nitrogen was excreted in the urine. The amount of lysine excreted in the urine was proportional to the intake.

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The Essential Amino Acid Requirements of Infants: Valine

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In previous publications,[1,2] we have discussed the need for precise knowledge of amino acid requirements and the methods of evaluating them. The present report deals with the evaluation of the valine requirement of the infant, and the technique employed has been that used in all our recent studies, namely, the use of a basal diet, the nitrogen moiety of which was supplied by a mixture of 18 L-amino acids * in the proportions found in breast milk. The intake of the amino acid under study was varied to determine the minimal quantity required to permit normal weight gain and nitrogen retention as well as the appearance of health. In each instance, as the amino acid under study was reduced it was replaced by glycine in order to keep the nitrogen intake constant.

Subjects

These studies were carried out on five normal male infants who were hospitalized for social reasons. They were between 1 and 5 months of age when these observations were made. The diet used in these studies was identical with that described elsewhere with the exception of the fat. For the last three infants corn oil † was used in place of a hydrogenated vegetable fat.‡ The diet was fed at a caloric level of 125 Cal. per kilogram to Infants A and E. It was necessary to give 140 Cal. per kilogram to Infants C, D, and B in order to obtain adequate weight gain. The technique of the metabolism studies and the analytical procedures used were as described in an earlier publication.[1] Individual protocols are given below.

Individual Protocols

BABY A.—This child was born Feb. 29, 1956 and weighed 3600 gm. at birth. At the beginning of the study he was six weeks old and weighed 4,990 gm. which placed him between the 50th and the 75th percentile. His course on different levels of valine intake is shown graphically in Figure 1.

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* The threonine in this mixture was supplied by Winthrop-Stearns, Inc.

† Mazola, supplied by courtesy of Corn Products Refining Company.

‡ Crisco, supplied by courtesy of Proctor and Gamble.

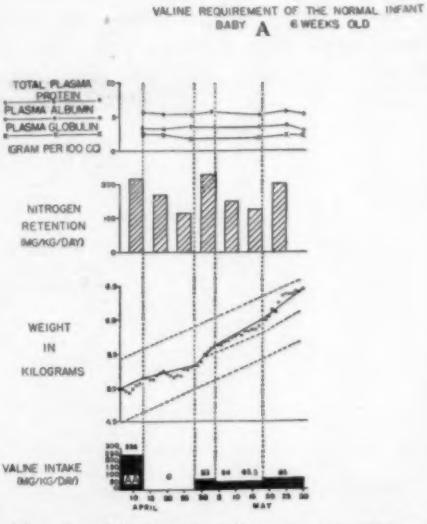

Fig. 1.—This baby's valine requirement was 85 mg/kg/day. The dotted lines represent the 50th, 75th, and 90th percentile curves.

It is apparent that the omission of valine from the diet for a period of two weeks was followed by a gradual reduction in nitrogen retention and by a slight reduction in the rate of weight gain. When valine was supplied at a level of 83 mg. per kilogram, a marked response was observed in both weight gain and nitrogen retention. Reduction of the valine intake to 63.5 and 64 mg. per kilogram caused some falling off of both the retained nitrogen and the weight gain. Improvement in the weight gain and normal nitrogen retention were again observed in the final period on an intake of 85 mg. per kilogram. His weight curve rose above the 75th percentile when he received adequate valine. It would thus appear that 85 mg. per kilogram was an adequate intake of valine for this baby.

BABY B.—This baby was born prematurely on Oct. 25, 1956, birth weight, 1,800 gm. His subsequent course was uneventful and he gained weight steadily. At the time the study was begun, he was six weeks old and weighed 3,100 gm.

As is shown in the accompanying graph (Fig. 2), the removal of valine from the diet resulted in a cessation of weight gain and a sharp reduction in nitrogen retention. The intake of 86 mg. per kilogram permitted good weight gain, but nitrogen retention was less than average. Weight gain and nitrogen retention were excellent both on the 126 and on the 105 mg. per kilogram intakes. Since the performance was quite as good on an intake of 105 mg. per kilogram as on the control periods in which 262 and 254 mg. of valine per kilogram were given, 105 mg. per kilogram was considered to be the requirement for Baby B.

Some reduction in plasma albumin was noted in Baby B during the valine-free period; this returned to normal with adequate supplementation.

BABY C (Fig. 3).—Baby C was born prematurely on Jan. 5, 1957, with a birth weight of 1,300 gm. He had an uneventful course in the premature unit. At the time the study was begun, he was 3½ months of age and he weighed 3,600 gm. The normal per-

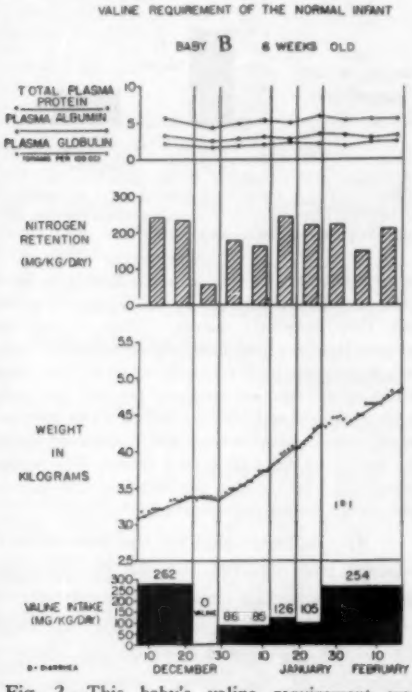

Fig. 2.—This baby's valine requirement was 105 mg/kg/day.

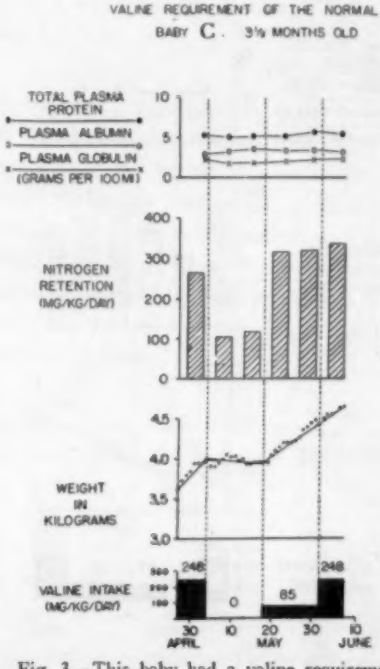

Fig. 3.—This baby had a valine requirement of 85 mg/kg/day.

centile weight curves cannot be used in evaluating his progress because of his extremely low birth weight. When valine was omitted from the diet of this baby and glycine substituted on an equal nitrogen basis, weight gain ceased and there was a marked reduction in nitrogen retention. Excellent weight gain and nitrogen retention occurred when valine was restored at a level of 85 mg. per kilogram per day. Performance at this level was quite as good as at the full level of valine intake, i. e., the amount found in breast milk.

BABY D (Fig. 4).—This baby was born Feb. 20, 1957, with a birth weight of 3,000 gm. He was a little over three weeks old and weighed 3,400 gm. when studies were commenced. His weight at this time placed him between the 3rd and 10th percentiles. Weight gain ceased and nitrogen retention was reduced when valine was removed from the diet and replaced by glycine. An intake of 105 mg. per kilogram per day permitted normal weight gain and nitrogen retention comparable to that on an intake of 260 mg. per kilogram per day. His weight curve remained at all times between the 3rd and 10th percentile curves.

BABY E (Fig. 5).—Baby E was born Dec. 6, 1956 weighing 3,300 gm. Studies were commenced

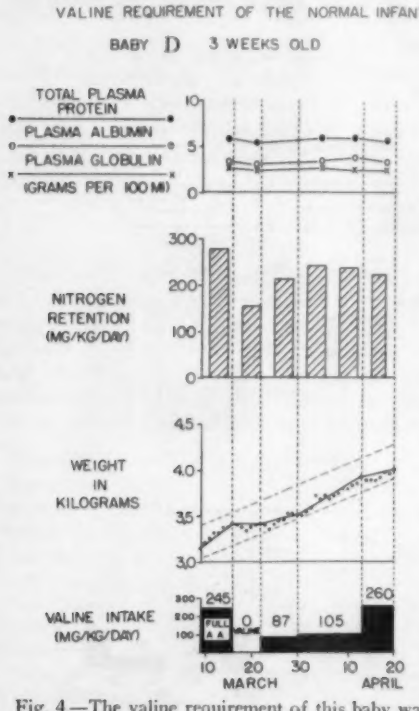

Fig. 4.—The valine requirement of this baby was 105 mg/kg/day. The dotted lines represent the 3rd and 10th percentile curves.

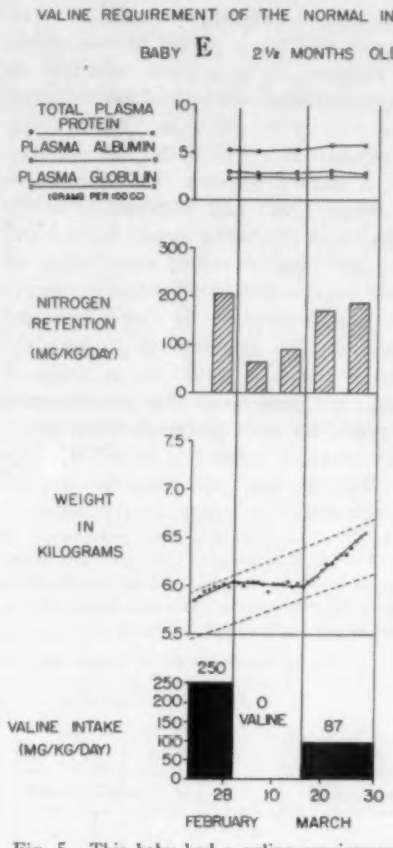

Fig. 5.—This baby had a valine requirement of 87 mg/kg/day. The dotted lines represent the 50th and 75th percentile curves.

at the age of 2½ months, at which time he weighed 5,800 gm. This weight placed him between the 50th and 75th percentile curves. When valine was omitted from the diet, some loss of weight occurred and there was poor nitrogen retention. A valine intake of 87 mg. per kilogram per day was sufficient to permit weight gain and nitrogen retention which were similar to that which occurred during the period of full amino acid intake. The weight curve remained between the 50th and 75th percentile curves throughout the study.

It thus appears that of the five subjects studied, two required 105 mg. per kilogram per day, whereas the requirements of the remaining three were satisfied by intakes of 83 to 87 mg. per kilogram per day. A summary of the valine intake in these studies is found in Table 1.

TABLE 1.—*Valine Intake of Each Infant*

Baby	Valine Intake, Mg/Kg/Day	
	Inadequate	Adequate
A	64	83
B	85	105
C	0	85
D	87	105
E	0	87

Clinical Observations

Specific symptoms attributable to valine deficiency were not observed in these studies. During the valine-free periods, however, a number of nonspecific symptoms were noted. The appetite was poor, there was a tendency toward drowsiness, and when the infants were awake, there seemed to be an unusual amount of irritability and crying. These symptoms disappeared with valine supplementation.

Laboratory Findings

A slight reduction of plasma albumin associated with a deficient intake of valine was noted in Babies B and E, and a slight reduction of globulin was noted in Baby A. The significance of these changes remains doubtful.

The metabolic data obtained on these infants are summarized in Tables 2 to 6. Periods of inadequate valine intake were characterized in the majority of instances by an increased urinary excretion of nitrogen. The fecal excretion of nitrogen remained relatively constant.

It was possible to establish quantitative amino acid urinary excretion patterns by column chromatography in only one subject (Baby D). The only consistent trend was in the amount of valine excreted. This was low during the period of zero intake, still lower during the next period, of 85 mg. per kilogram per day intake, which was inadequate for this child, and then rose when adequate valine (105 mg. per kilogram per day) was provided. These figures are summarized in Table 7.

TABLE 2.—*Metabolic Data, Baby A*

Date	4/9-12	4/16-19	4/23-26	4/30-5/3	5/7-10	5/14-17	5/21-24
Valine intake, mg/kg/day	206	0	0	83	64	63.5	85
Av. wt., kg.	5.08	5.20	5.23	5.50	5.72	5.88	6.22
Nitrogen intake, gm/day	2.43	2.64	2.72	2.70	2.78	2.82	2.92
Nitrogen in urine, gm/day	1.17	1.62	1.90	1.26	1.76	1.80	1.46
Nitrogen in stool, gm/day	0.17	0.15	0.20	0.17	0.16	0.17	0.19
Nitrogen retention, mg/kg/day	216	167	119	231	150	127	201
Plasma protein, gm/100 ml.							
Total	5.78	5.48	5.32	5.73		5.34	5.82
Albumin	3.34	3.22	3.55	—		3.48	3.61
Globulin	2.44	2.26	1.77	—		1.86	2.21

TABLE 3.—*Metabolic Date, Baby B*

Date	12/10-13	12/17-20	12/24-27	12/31-1/3	1/7-10	1/14-17	1/21-24	1/28-31 *	2/4-7	2/11-14
Valine intake, mg/kg/day	202	202	0	86	85	126	105	254	254	254
Av. wt., kg.	3.20	3.34	3.36	3.47	3.68	3.96	4.21	4.49	4.59	4.74
Nitrogen intake, gm/day	1.59	1.63	1.71	1.71	1.78	1.90	2.03	2.13	2.26	2.30
Nitrogen in urine, gm/day	0.72	0.71	1.44	0.89	1.04	0.83	1.01	0.66	1.08	1.14
Nitrogen in stool, gm/day	0.10	0.15	0.08	0.21	0.15	0.09	0.09	0.47	0.50	0.16
Nitrogen retention, mg/kg/day	242	232	56	177	160	247	220	223	148	211
Plasma protein, gm/100 ml.										
Total	5.54		4.28	4.96	5.24	4.98	5.88	5.14	5.30	5.42
Albumin	3.40		2.54	2.99	3.05	2.67	3.59	3.17	2.92	3.02
Globulin	2.14		1.74	1.97	2.19	2.31	2.29	1.97	2.47	2.40

* Diarrhea during this period until first day of next period.

TABLE 4.—*Metabolic Data, Baby C*

Date	4/29-5/2	5/6-9	5/13-16	5/20-23	5/27-30	6/3-6
Valine intake, mg/kg/day	248	0	0	85	85	248
Av. wt., kg.	3.89	3.98	3.96	4.13	4.27	4.43
Nitrogen intake, gm/day	1.83	1.99	1.68	2.02	2.11	2.25
Nitrogen in urine, gm/day	0.68	1.48	1.10	0.56	0.56	0.62
Nitrogen in stool, gm/day	0.12	0.10	0.13	0.15	0.15	0.14
Nitrogen retention, mg/kg/day	264	103	114	316	320	335
Plasma protein, gm/100 ml.						
Total	5.28	5.04	5.24	5.45	5.74	5.65
Albumin	2.98	3.24	3.54	3.42	3.43	3.23
Globulin	2.30	1.80	1.70	2.03	2.31	2.42

TABLE 5.—*Metabolic Data, Baby D*

Date	3/11-14	3/18-21	3/25-28	4/1-4	4/8-11	4/15-17
Valine intake, mg/kg/day	245	0	87	105	105	260
Av. wt., kg.	3.32	3.37	3.48	3.63	3.79	3.91
Nitrogen intake, gm/day	1.56	1.56	1.72	1.75	1.87	1.93
Nitrogen in urine, gm/day	0.53	0.92	0.80	0.76	0.85	0.95
Nitrogen in stool, gm/day	0.11	0.11	0.18	0.12	0.13	0.13
Nitrogen retention, mg/kg/day	278	158	214	240	236	218
Plasma protein, gm/100 ml.						
Total		5.38		5.98	5.85	5.57
Albumin		3.08		3.47	3.51	3.24
Globulin		2.35		2.51	2.34	2.33

TABLE 6.—*Metabolic Data, Baby E*

Date	2/25-28	3/4-7	3/11-14	3/18-21	3/25-28
Valine intake, mg/kg/day	250	0	0	87	87
Av. wt., kg.	5.98	6.03	6.01	6.14	6.43
Nitrogen intake, gm/day	2.72	2.72	2.51	2.92	3.06
Nitrogen in urine, gm/day	1.23	2.16	1.84	1.67	1.67
Nitrogen in stool, gm/day	0.25	0.15	0.13	0.21	0.21
Nitrogen retention, mg/kg/day	206	71	89	170	183
Plasma protein, gm100 ml.					
Total	5.61	5.04	5.21	5.72	5.64
Albumin	3.54	2.77	2.83	3.16	3.06
Globulin	2.07	2.27	2.38	2.56	2.58

TABLE 7.—*Urinary Valine Excretion, Baby D*

Date	3/18-22	3/25-28	4/8-12
Valine intake, mg/kg/day	0	87	105
Valine excretion, mg/kg/day	0.18	0.06	0.50
Total identified amino acids, mg/kg/day	35	30	43

Comment

These data indicate that valine intakes ranging between 85 and 105 mg. per kilogram per day are adequate to maintain normal infant growth and health. Since these figures were obtained by the use of a completely synthetic diet, the question arises of whether the valine requirement is of the same order of magnitude when a natural diet is fed. From studies that we have carried out on the minimal protein requirements of infants, using a cow's milk formula, we have been able to conclude that the valine requirement is certainly not higher than 85-105 mg. per kilogram per day. In these studies, the amount of milk was reduced while the total caloric intake was kept constant. Four infants have gained weight well and retained adequate amounts of nitrogen when only 4% of the

calories were provided in the form of cow's milk protein and the formula was supplemented by unessential nitrogen in the form of either urea or glycine. Calculation of the valine intake of these infants from available analyses of milk protein[3] gives a valine intake in the range of 80 mg. per kilogram per day.

Infants receiving the usual cow's milk formulae would receive at least twice as much valine as required. Hence there would not seem to be any need for valine supplementation of the formulae of normal infants. However, it is quite possible that certain pathologic states may increase the valine requirement.

Summary

The valine requirement of the normal infant was determined by the use of a synthetic diet, the nitrogen moiety of which was composed of 18 L-amino acids. Our criteria of normal growth were satisfied by an intake of 85 mg. per kilogram of body weight per day in three infants and of 105 mg. per kilogram of body weight per day in the other two.

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The Arginine Requirement of the Infant

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The role of arginine in nutrition has not as yet been completely defined. It is essential for growth in some animals, required for optimal growth in others, while in still others it does not seem to be at all necessary for growth. Arginine is required for growth by the turkey poult [1] and the chick,[2] the requirement being especially high during the first few weeks of life. This high requirement is due to a complete inability to synthesize arginine; in fact, the young fowl is unable to synthesize arginine even when ornithine is provided.[3] Both young rats [4] and weanling pigs [5] can grow at subnormal rates without arginine, but it is necessary for optimal growth. Apparently the synthesis of arginine cannot proceed rapidly enough or in large enough amounts to provide for the rapid growth of these animals. The young mouse [6] seems to grow well on diets that do not contain any arginine.

Arginine has been regarded by some workers as being unessential for the adult rat,[7] the dog,[8] and the adult human male,[9] since positive nitrogen balance can be maintained on diets devoid of arginine. However, in the studies of Holt et al.[10-12] in young men, there was a striking diminution in spermatozoa count after nine days of arginine deprivation; this occurred in subjects who were in positive nitrogen balance. This group confirmed their findings in rats; degenerative changes in the testes were noted within three weeks of arginine withdrawal. However, degenerative changes in the testes have not been uniformly found in arginine deprivation. Neither Williams and Watson [13] nor Cannon [14] was able to confirm this finding in the rat. Two different Japanese workers,[15,16] however, were able to demonstrate testicular degeneration in the rat after prolonged periods of arginine withdrawal. None of the men studied by Rose [17] showed any reduction in sperm count when arginine was withheld for as long as 64 days. These conflicting findings of the effect of arginine deprivation on the testes indicate the need of further work to clarify this particular facet of the metabolic role of arginine.

This present study was designed to determine if arginine is a dietary essential for the growing human infant.

All metabolic and laboratory procedures were identical with those used in our previous studies in the amino acid requirements

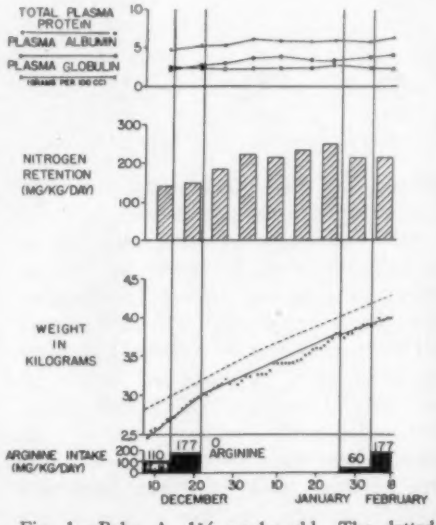

Fig. 1.—Baby A, 1½ weeks old. The dotted line represents the 3d percentile curve.

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Department of Pediatrics, New York University-Bellevue Medical Center.

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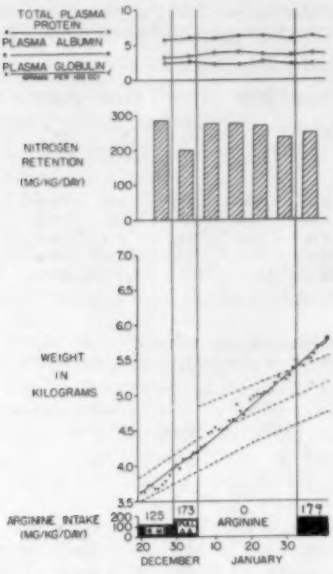

Fig. 2.—Baby B, 3 weeks old. The dotted lines represent the 25th, 50th, and 75th percentile curves.

of infants.[18,19] Our subjects were three normal male infants who ranged in age from 1½ weeks to 3½ months and in weight from 2.5 to 4.6 kg. at the start of the study. One baby (Baby A) was fed 125 Cal. per kilogram per day; 140 Cal. per kilogram was required by the other two infants.

The plan of study was to have a control period during which the full complement of amino acids was fed and then to remove the arginine completely. Nitrogen intake was kept constant by the substitution of glycine for the arginine. Two of these infants also had a control period on a natural diet; one on an evaporated milk formula and the other on pooled breast milk.

Individual Protocols

Baby A (Fig. 1).—Negro, born Nov. 26, 1956, birth weight 2.5 kg. He remained in the hospital for social reasons and had just regained his birth weight when he was admitted to the study. This weight was just beneath the 3d percentile curve. Although his weight gain was adequate during his two control periods on an evaporated milk formula and full amino acid diet, his nitrogen retention was less than at any subsequent time. This was presumably due to his very young age. Arginine was withdrawn from this baby's diet for 35 days. During this time, he gained weight consistently, staying at all times just under the 3d percentile curve. His nitrogen retention remained excellent during this period of time, in the same range as it was during the control period at the end of the study when he received a full complement of arginine.

Baby B (Fig. 2).—Negro, born Dec. 6, 1956, birth weight 3.3 kg. He remained in the hospital for social reasons and weighed 3.7 kg. at the age of 2½ weeks, when he became a subject in the study. This weight was between the 25th and 50th percentile curves. Arginine was completely removed from his diet for a period of 28 days. His weight gain was such during this period that his curve rose to between the 50th and 75th percentile curves. Nitrogen retention was as satisfactory during this period of arginine deprivation as it was during the control periods at the beginning and end of the study.

Baby C (Fig. 3).—Negro, born prematurely Oct. 25, 1956, birth weight of 1.8 kg. After he had gained sufficient weight to be discharged from the premature unit, he remained in the hospital for social reasons. He was 3½ months old and

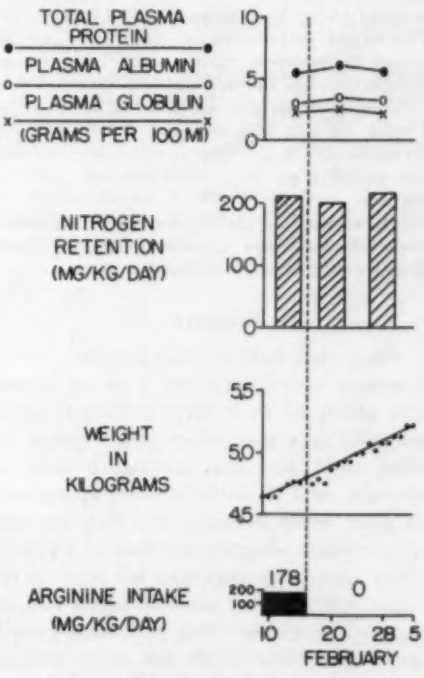

Fig. 3.—Baby C, 3½ months old.

TABLE 1.—*Baby A, Metabolic Observations*

	Date								
	12/10-13	12/17-20	12/24-27	12/31-1/3	1/7-10	1/14-18	1/21-24	1/28-31	2/4-7
Arginine intake, mg/kg/day	110	177	0	0	0	0	0	60	177
	Evaporated milk								
Av. wt., kg.	2.62	2.89	3.08	3.20	3.35	3.45	3.66	3.82	3.98
Nitrogen intake, gm/day	1.29	1.40	1.52	1.63	1.69	1.74	1.81	1.89	1.93
Nitrogen in urine, gm/day	0.67	0.86	0.78	0.74	0.82	0.79	0.77	0.83	0.93
Nitrogen in stool, gm/day	0.25	0.11	0.17	0.18	0.13	0.14	0.13	0.24	0.14
Nitrogen retention, mg/kg/day	141	150	188	226	216	236	250	214	215

TABLE 2.—*Baby B, Metabolic Observations*

	Date						
	12/24-27	12/31-3	1/7-10	1/14-17	1/21-24	1/28-31	2/4-7
Arginine intake, mg/kg/day	125	173	0	0	0	0	179
	Breast milk						
Av. wt., kg.	3.72	4.06	4.44	4.75	4.99	5.19	5.50
Nitrogen intake, gm/day	1.84	1.93	2.10	2.26	2.36	2.49	2.64
Nitrogen in urine, gm/day	0.59	0.93	0.73	0.80	0.88	1.11	1.12
Nitrogen in stool, gm/day	0.18	0.19	0.15	0.15	0.13	0.18	0.16
Nitrogen retention, mg/kg/day	288	199	275	275	270	238	248

weighed 4.6 kg. when he was included in the study. His weight performance on study could not be judged by percentile curves, since these are applicable only to full-term infants. Arginine was removed from his diet for a period of 14 days. During this time he continued to gain weight and retain nitrogen at the same rate as during the control period when he received the full quota of arginine.

No changes in metabolic data were discernible during the periods of arginine withdrawal. These data are summarized in Tables 1 to 3.

Comment

These data indicate that arginine is not a dietary essential for the growing infant. The ability of these three infants to grow normally at a time when infant growth is most rapid, to retain normal amounts of nitrogen, and to manifest every appearance of good health indicates that they are able to synthesize adequate amounts of arginine. Since spermatogenesis does not occur in infancy, this does not place an added load on arginine synthesis. This continued growth without arginine is all the more striking when compared with our other studies on the essential amino acid requirements of infants. In all of these, the withdrawal of an essential amino acid resulted in an arrest of growth within 48 hours.

It is possible of course, that certain pathologic states may so raise the arginine requirement that synthesis may not be rapid enough to fulfill the requirement. This particular aspect of the arginine requirement deserves further study.

Summary

Three normal male infants were fed diets of arginine for periods of 14 to 35 days. All three gained weight well, re-

TABLE 3.—*Baby C, Metabolic Observations*

	Date		
	2/11-14	2/18-21	2/25-28
Arginine intake, mg/kg/day	178	0	0
Av. wt., kg.	4.74	4.83	5.04
Nitrogen intake, gm/day	2.30	2.36	2.42
Nitrogen in urine, gm/day	1.14	1.26	1.18
Nitrogen in stool, gm/day	0.16	0.13	0.16
Nitrogen retention, mg/kg/day	211	200	215

tained adequate amounts of nitrogen, and appeared to be in excellent health. Under the conditions of this study, arginine does not seem to be a dietary essential for the normal growing infant.

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Cystinuria in Mentally Retarded Siblings with Atypical Osteogenesis Imperfecta

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Cystinuria is a hereditary disorder of renal function in which defective tubular reabsorption of the amino acids cystine, lysine, arginine, and ornithine leads to the excretion of large amounts of these substances in the urine. The only reported clinical consequence has been formation of renal stones composed of cystine. As a result of the limited solubility of cystine, precipitation may occur when the concentration in urine exceeds the solubility. Cystine stones are generally found only in persons excreting at least 250μg. of cystine per milligram of creatinine.[1]

Two patterns of inheritance have been noted.[2] All homozygous persons excrete cystine, lysine, arginine, and ornithine. In Type I families the trait is completely recessive, and the heterozygous parents show no defect in excretion of cystine. In Type II families the condition is "incompletely recessive," and the trait is manifested in the heterozygous person by increased excretion of cystine and lysine without excretion of arginine and ornithine. The most likely explanation for the presence of two types of inheritance, distinguishable only by phenotype of the parent, would seem to be two mutant conditions, or alleles, of the same gene.[3]

During an investigation of urinary excretion patterns among related mentally retarded persons in Muscatatuck State School, Butlerville, Ind., I encountered a group of siblings exhibiting the characteristic excretion pattern of cystinuria. The excretion of lysine, arginine, ornithine, and cystine in urine of five siblings is shown in the Table.

*Familial Excretion of Lysine, Arginine, Ornithine, and Cystine**

Sibling	Age, Yr.	Lysine	Arginine	Ornithine	Cystine
A	16	25	—	—	22
B	6	360	50	45	100
C	9	1,010	108	280	250
D	11	70	—	—	37
E	14	300	70	140	100
Controls (6)		27	—	—	—

* Data given in μg/mg. creatinine.

Three of the five children, Siblings B, C, and E, excreted lysine, arginine, ornithine, and cystine in large amounts. Cystine was detected in urine of all five children, although excretion of lysine by Siblings A and D was within normal limits. Excretions of leucine, valine, glutamic acid, serine, glycine, threonine, alanine, glutamine, tyrosine, and histidine were in the normal ranges in all five children. No sugar or protein was present in the urine specimens. Blood specimens from each of the five children were examined; there was no elevation in the concentrations of lysine, arginine, or cystine in serum. Siblings B and C were observed earlier to have an atypical form of osteogenesis imperfecta without blue sclerae.[4] A third child, Sibling E, showed radiologic changes consistent with the diagnosis of osteogenesis imperfecta, but he had had no fractures. The normal low excretion of all amino acids except cystine, lysine, arginine, and ornithine, together with the absence of sugar, serves to distin-

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From The Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

guish these children from those persons with cystine excretion, rickets, and osteomalacia as significant findings in the Fanconi syndrome.[5] In the latter disease there is a generalized amino-aciduria, glycosuria, and proteinuria.

The coincidence of excessive excretion of cystine, lysine, ornithine, and arginine by the three siblings who exhibit skeletal changes warrants careful investigation to determine possible relation of the defects. The most severely afflicted child, Sibling C, also exhibited the largest excretion of amino acids. We have as yet been unable to obtain urine specimens from the parents in order to elucidate the type of inheritance. The mother of the children was found to have an I. Q. of about 50. It was thought that her own father was also the father of her 11 children, 5 of whom survive and are discussed here.

Summary

Three of five mentally retarded children in one family excreted cystine, lysine, arginine, and ornithine in amounts characteristic of cystinuria. Blood concentrations of these amino acids were normal, as were urinary excretions of other amino acids. The same three children exhibited a form of osteogenesis imperfecta without blue sclerae.

Children's Hospital (*29*).

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Purpura Fulminans

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Infection is an important cause of purpura in infants and children. The purpuric manifestations of infectious diseases such as rubeola, varicella, infectious mononucleosis, tuberculosis, or cat scratch fever may be of interest to the physician as merely a visible suggestion of host sensitization to a bacterial or viral antigen. Following cases of scarlet fever or rubeola or with a meningococcal sepsis, there can occur a rare and overwhelming form of purpura rapidly causing death. This severe confluent purpura results in local tissue death and forms the clinical syndrome of purpura fulminans or purpura gangrenosa.

Guelliot [1] first recorded its description in 1884. Approximately 100 cases of this syndrome have been reported in the literature with a mortality rate of 92%. Purpura fulminans is a rare complication of scarlet fever, having been seen only 4 times in over 72,000 cases observed by several groups of authors.[2,3] We feel that the following case report is of interest because purpura fulminans followed scarlet fever, the patient survived, and this case is the first instance of survival with steroid therapy.

The characteristics of this illness and its autopsy findings are remarkably similar in the literature. It occurs in young people. It may begin about two weeks following the onset of a mild scarlet fever. Massive ecchymoses develop with intense systemic symptoms of chills, fever, vomiting, and prostration. Cerebral symptoms, hemorrhagic shock, coma, and death ensue as the purpura expands. During the first 48 hours, the ecchymoses become larger and are symmetrically grouped on the lower extremities as well as over points of pressure on the sacrum, buttocks, and iliac crests. The lesions, port wine in color, form blisters that discharge a sanguinous fluid on the hard edematous skin surface. Gangrene develops as necrosis and eschar formation change the color to a bluish black. The toes, fingers, nose, and cheek areas are particularly prone to dry gangrene. During the next two to three weeks, a period of slough and separation follows, demarcating the ischemic areas from the surrounding healthy skin. Repair then begins with granulation and scar formation. The majority of patients die during the first few days of the illness; thus purpura fulminans rarely progresses to purpura gangrenosa.

Microscopically, there is necrosis of arteries and veins in the skin and viscera. Many vessels are occluded by thrombi and are surrounded by exudate containing large numbers of neutrophils. Extravasation of blood is seen in the areas where blood vessel necrosis is complete.[4]

The diagnosis must be a clinical one. Laboratory findings vary from case to case, although many show a thrombocytopenia. The bleeding time is usually prolonged, as is the coagulation time. Prothrombin times are abnormal, but the Rumpel-Leede test of capillary fragility may be normal. In one recent report, a deficiency of Factor V was found to be present.[5]

The possibility of hemorrhage into the adrenal cortices in such a fulminating disturbance must be borne in mind. The laboratory evidence of the bleeding tendency seems often to be equivocal and cannot explain the shock and massive exsanguination into the subcutaneous tissues.

Report of a Case

History.—A 9-year-old white girl was admitted to the Jackson-Madison County General Hospital

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From The Children's Clinic and Jackson Clinic.

Fig. 1.—Right ankle at time of admission, July 19, showing large ecchymosis and numerous petechiae.

on July 19, 1956, because of purpura and ecchymotic areas over the lower extremities. She had been entirely well until three weeks before admission. At that time, she had had a high fever, vomiting, tonsillitis, and a developing fine red rash which subsequently desquamated. Her family physician was consulted, and chloroamphenicol in small doses was given to her for several days. The fever continued, and enlargement of the cervical lymph nodes was noted. Twenty-four hours prior to admission, petechiae were seen for the first time. She was given one 250 mg. capsule of novobiocin and was referred to this hospital.

Physical Findings.—On admission, the examination revealed an acutely ill child with pallor of the skin, temperature 104 F orally, pulse rate 120 per minute, and blood pressure 80/60. In addition to evidence of recent weight loss, tonsillitis, and moderate cervical adenopathy, the striking findings were limited to the skin: Both legs were swollen and covered with small petechiae and large ecchymoses over the entire left leg and ankle. Both ankles were covered by solid ecchymosis with a sharp serpentine border separating it from the uninvolved skin (Fig. 1).

Laboratory Findings.—Initial laboratory examinations included 4,560,000 RBC, hemoglobin 16.5 gm. per 100 cc., and 11,450 WBC. There were 10% stab forms, 82% segmented neutrophils, and 8% mature lymphocytes, and the smear showed an apparent decrease in the number of platelets. Bleeding time was greater than 15 minutes (normal, 1 to 3 minutes). Clotting time was four minutes (normal by the capillary tube method). The prothrombin time was 16 seconds, with a 13-second control. The urine was normal, serology negative, and Rumpel-Leede test normal on several occasions. The patient's blood was Type A, Rh-positive. Throat culture done on admission grew out a pure culture of β-hemolytic Streptococcus.

Hospital Course.—Four hours after admission, the child was found to be in severe hemorrhagic shock with unobtainable pulse and blood pressure. She was pale and sweating but alert and complaining of extreme thirst. The ecchymotic areas had spread to involve symmetrically the lower legs,

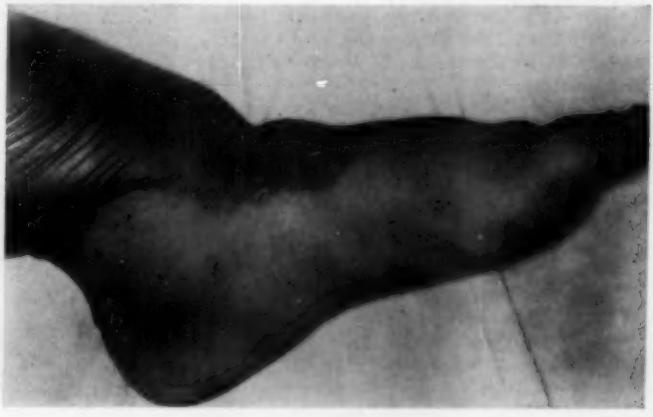

Fig. 2. — View of right ankle, July 20, demonstrating blister formations of previous ecchymotic area.

feet, and left thigh. The skin revealed normal islands scattered in the otherwise solid purpuric areas. Peripheral pulsations were normal.

Therapy consisted of intravenous levarterenol bitartrate, whole blood, and hydrocortisone sodium succinate, in addition to massive doses of crystalline penicillin. Fifteen hundred cubic centimeters of whole blood was given slowly during the ensuing 24 hours, and the patient's condition improved.

On July 20, the second hospital day, the patient was alert and taking oral fluids; no extension of the purpura was noted. Bleeding time was six minutes; the platelet count was 40,000/cu. mm., or about 8/1,000 RBC on smear. The hemoglobin was 15 gm/100 cc. At no time had any bleeding been observed from the gastrointestinal tract, and on July 22 a stool was chemically negative for blood.

Fig. 3.—View of left foot, Oct. 30, demonstrating dry gangrene with spontaneous amputation of toes.

The admission blood culture was reported as showing no growth after one week's observation.

By July 23, while the patient was still on steroid therapy, the platelet count reached 480,000, and by July 26 it was 507,000. Bleeding time became normal by July 23, and determinations were not repeated after that date.

The skin of the lower extremities demonstrated no advance of ecchymosis 12 hours after the beginning of steroid treatment. These areas, however, were showing early slough and blister formation by July 20 (Fig. 2). On Aug. 2, the patient exhibited partial-thickness loss of skin over large areas of the left thigh, legs, and dorsum of the feet. A portion of all the toes of the right foot exhibited dry gangrene of the distal and inferior portions. There were scattered areas of full-thickness skin loss covered by thick black eschar on the left thigh and the legs. The left leg and foot showed large areas of skin loss with dry

Fig. 4.—Picture showing healing of previously described lesions five weeks after onset (Aug. 28).

gangrene of the distal half of the lateral three toes. No secondary infection was evident. No grafting was felt to be necessary. The toes were allowed to heal and slough without excision (Fig. 3). The involved areas were treated as a "burn" with hexachlorophene (pHisoHex) baths, dry and nitrofurazone dressings, and gradual debridement.

During the month of hospitalization, the patient remained febrile, presumably owing to the presence of skin necrosis. Otherwise, she did well and was given supportive therapy consisting of oral iron, high-protein diet, tetanus antitoxin, and antipyretics. Hydrocortisone therapy was given for the first five days only. The 100 mg. initial intravenous dose

Fig. 5.—Completed healing of left thigh seven weeks after onset of illness (Sept. 11).

was followed by an oral dose every six hours in gradual tapering amounts. Penicillin was continued for a 10-day period followed by administration of tetracycline for 15 days. Figures 4 and 5 show the final result.

Follow-up examinations on this child for the past 18 months have revealed no hematological abnormalities. She is well and attending school.

Comment

It is of interest in this case that both the mother and father of the child were found to be healthy carriers of the Streptococcus in their nasopharynx. During the patient's illness, a brother was treated for a peritonsillar abscess, and throat culture also revealed β-hemolytic Streptococcus. He had no purpura, but his Rumpel-Leede test was positive. A blood smear revealed a decreased number of platelets during the acute part of his illness. These streptococci were not typed. It would seem reasonable that this particular Streptococcus could have possessed a toxin specifically causing a platelet suppression.

The etiology of purpura fulminans remains obscure. Its relation to the Shwartzman phenomenon has been discussed by previous authors.[6] In addition to the vasculitis in these cases, the platelet suppression may also be important, as demonstrated in this patient. Current hematological textbooks place this syndrome in the nonthrombocytopenic type of purpura in classification.[7] This appears to be justified neither by a review of the literature nor by the case here presented; however, the basic pathological lesion of vasculitis and gross bleeding into the tissues is usually absent in a typical thrombocytopenic purpura.

Steroid therapy has been reported previously in a surviving case of thrombocytopenic purpura following rubeola.[8] Bleeding manifestations in this case, however, were limited to a hemorrhagic character of the measles rash, epistaxis, and hematuria. As far as we are able to ascertain, this is the second recorded use of the steroid hormone in this syndrome.[9] It is the first surviving case so treated.

The prompt and dramatic response of purpura fulminans in this case far outweighs the very real danger of adrenal cortical hormone use in the presence of active infection. Survival in this usually fatal condition depends on early diagnosis and prompt adequate therapy.

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Pulmonary Hypertension and Vascular Change in Patients with Congenital Heart Disease

A Review of the Literature

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The natural history of pulmonary hypertension and pulmonary vascular change in patients with certain forms of congenital heart disease is a subject of utmost importance in light of advanced surgical techniques which now allow for surgery for almost any type of cardiac lesion. The optimal age for surgical intervention for many of the cardiac lesions is not known, but one of the more important factors to be considered is the vascular change resulting from abnormal amounts of pulmonary blood flow and pressure. Severe histologic changes may be irreversible or may greatly increase the risks of surgery. The following is a review of the pertinent literature and present thinking of workers in this field.

Welch [1] in 1947 studied the pulmonary changes in 67 patients with congenital heart disease consisting of patent ductus arteriosus (PDA), interatrial septal defect (IASD), and interventricular septal defect (IVSD). A control series of 10 noncardiac patients from each of the first seven decades of life served as a base line for the normal pulmonary changes with age.

He classified small muscular arteries into three groups based on their external diameter. Medial thickening, intimal proliferation, and intimal hyalinization were graded 1+ to 4+ according to the extent of change. In all controls after the fourth decade, small muscular arteries showed mild intimal changes and some degree of atherosclerosis. By the seventh decade, these intimal changes were consistently graded 2+ to 3+. No normal children under 10 years of age showed these changes.

In 25 cases of PDA where the diameter ranged from 3 to 15 mm., only 1 showed more pulmonary vascular change than the controls. This patient had severe intimal hyalinization and pulmonary atherosclerosis associated with a PDA of 13 mm. diameter. Welch stated, "It would appear that there is no constant relation between either the diameter of the ductus or calculated volume flow and the degree of pulmonary hypertension."

He found no correlation between the size of the ductus, the circumference of the pulmonary artery, and the thickness of the right ventricle. Others have suggested that these measurements can be used as criteria for calculating pulmonary hypertension.

Twenty-five cases with IASD greater than 0.8 cm. in diameter and 17 with a defect greater than 2 cm. were similarly studied. In no case was the pulmonary change greater than in the controls.

Of 11 cases of IVSD ranging from 0.4 to 2 cm., only 1 had changes greater than the controls. Marked intimal changes in this case were associated with a defect 2 cm. in diameter.

Welch concluded that the pulmonary vascular bed plays a passive role in patients with increased pulmonary blood flow, except in those conditions in which venous return is impeded, as in left heart failure or mitral stenosis.

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Swan [2] in 1949 reported a case which was preoperatively diagnosed as coarctation of the aorta with a distal PDA. The PDA was ligated without finding a coarctation; postoperatively the patient developed right heart failure and died. At autopsy, congenital mitral stenosis with a hypoplastic left ventricle and aorta was seen. Microscopic lung findings showed marked medial hypertrophy and intimal thickening which had produced sufficient pulmonary resistance to cause reverse flow in the ductus so that ligation of the PDA resulted in right heart failure. Their conclusion was that had the correct diagnosis been made preoperatively, surgery would have been contraindicated.

Since 1950, Edwards [4] and his co-workers have contributed significantly to the problem of structural changes in the pulmonary vascular bed in patients with congenital heart disease. He first described three basic types of pulmonary arteries. The first type of artery was of the elastic type with numerous laminations of elastic tissue in the media, a moderate amount of adventitia, and a one-cell-layer intima. The second included the muscular arteries, which vary in size and are located near the smaller bronchi and bronchioles; in these, the media is muscular, with an internal and external elastic lamina. In normal adults the media is thin and the lumen wide. The third type of artery, the arteriole, is difficult to distinguish from the venule, since there is no muscle, only endothelium with a small amount of connective tissue near the alveoli.

Edwards found that, with increased pulmonary blood flow, changes, especially medial hypertrophy, occur primarily in the muscular arteries while the arterioles remain normal. This medial hypertrophy resembles closely the fetal vasculature, and it has been suggested by Edwards and others that this may represent a carry-over from fetal life. Civin [9] and Edwards have demonstrated that fetal muscular arteries have a narrow lumen and a thickened media. This may represent the necessary situation to maintain sufficient pulmonary vascular resistance to enable the fetal right ventricle to function as a systemic ventricle and to supply blood through the ductus arteriosus to the descending aorta. By the time the infant is 6 months of age, muscular arteries show a wide lumen and thin media, with the intima remaining unchanged. Changes in pulmonary resistance and flow may reflect the status of pulmonary arteries.

Although medial hypertrophy may act as a protective mechanism against the increased pulmonary blood flow with shunts from left to right, such anatomical alterations may progress to become detrimental. This point is generally believed to be reached when severe intimal changes also occur. A pathologic state exists when the lumen is fixed in a rigid state and the pulmonary resistance is markedly elevated.

Edwards [25] has expanded this concept of pulmonary resistance to blood flow by categorizing the type of vascular change and attempting thereby to predict the outcome of anticipated surgery. His "high resistance-high reserve" category includes muscular arteries with thick media, small lumen, and normal intima. These vessels therefore are still capable of vasoconstriction and of vasodilatation. Since they are not fixed in a rigid state, surgical correction of the lesion responsible for the increased pulmonary flow allows dilatation, with a decrease in pulmonary vascular resistance.

The category of "high resistance-low reserve" includes those vessels with intimal hyalinization and narrow lumen as well as medial hypertrophy. These often involve the larger arteries (3 mm. or wider in diameter), which supply a relatively wide segment of the lung. The distal vessels supplied by these may appear atrophic with dilated lumina, probably due to poststenotic changes. Therefore, in interpreting microscopic sections, it is important to search in several areas for such intimal changes to avoid being misled by these dilated vessels distal to the involved segment. These intimal lesions of large muscular arteries are specific for pulmonary hypertension of severe degree and chronic nature. Surgical correction of the "high resistance-high

reserve" type of situation results in a decrease in pulmonary vascular resistance and a normal physiologic state. After closure of a shunt in which "high resistance-low reserve" change has occurred, pulmonary hypertension may persist or even increase, with ensuing right heart failure.

A method of differentiating the type of involvement preoperatively has been suggested by Edwards,[25] involving determination of the ratio between the total pulmonary resistance and the systemic resistance. Measurements are made with the patient first breathing air and then breathing 100% oxygen. In 15 patients so tested with microscopic correlation, 4 were found to have an inflexible vascular bed and 11, a flexible vascular bed. In all cases of the flexible type, the ratio was reduced when 100% oxygen was administered.

With "high resistance-high reserve" type, the ratios varied but none were above 0.7 (pulmonary resistance did not exceed systemic). Administration of 100% oxygen resulted in a significant decrease in pulmonary compared to systemic resistance, with ratios consistently below 0.4.

With "high resistance-low reserve" type, the pulmonary resistance approached, equaled, or exceeded systemic resistance. Administration of pure oxygen resulted in a mild decrease in pulmonary resistance, the ratio never falling below 0.6 and more often approximating 1.

Heath and Whitaker[23] feel that pulmonary hypertension is an independent disease, incidental to and not correlated with congenital heart disease. This concept is based primarily on the lack of correlation between the degree of pulmonary vascular change and the size of the cardiac defect as studied by these workers. On the other hand, the data of Dammann[13,22] support such a correlation in congenital heart disease. In all of his reviewed cases of patent ductus arteriosus with pulmonary changes of significant magnitude, the patent ductus arteriosus was of sufficient diameter to allow transmission of systemic pressures into the lungs. Cases with a small patent ductus arteriosus never developed marked pulmonary hypertension. He[22] describes a case of stenosis of the left pulmonary artery associated with a large interventricular defect allowing decreased flow through the left lung field and systemic pressures in the right lung. Typical changes of pulmonary hypertension were seen in the right lung, while the left remained normal.

Dammann's[21,22] work, reported in July, 1956, has offered probably the most objective and significant evidence to date to demonstrate the causal relationship between increased pulmonary blood flow and the development of pulmonary hypertension.

He first studied the lungs from 100 patients with normal hearts ranging in age from newborn to about five years. An arbitrary method of measuring vessel changes was chosen. Only small muscular pulmonary arteries were used (easy to confuse with bronchial arteries). The total diameter was measured, then the diameter of the lumen. The ratio of the diameter of the lumen to two times the media plus the intima gave the lumen-size-to-wall-thickness ratio.

He found that at birth these small muscular pulmonary arteries have a rather small lumen-to-wall ratio and resemble closely those of a similar size of the systemic circulation. By 4 weeks of age, the lumen becomes relatively and absolutely larger and the media thins out. By 6 months of age, these changes progress to the stage seen in 5-year-olds, in that the muscular arteries appear much like venules. These changes occur rapidly at first and are marked at 6 months, but lumen dilatation continues slowly until early adulthood. Lind and Wegelius[26] showed that, in the human fetus, the right heart supplies the descending aorta by way of the ductus arteriosus. For this to be possible, the pulmonary vascular resistance must be equal to or greater than the systemic. The high pulmonary vascular resistance in the fetus seems related to the appearance of a small lumen-wall ratio, but the stimulus for this re-

sponse is obscure. Some have supposed that it is due to the collapsed lung per se and that expansion of the lungs with air and clamping of the umbilical artery causes an immediate fall in pulmonary vascular resistance below systemic with cessation of a right-to-left shunt via the patent ductus arteriosus. The work of Adams and Lind [20] showed that a left-to-right shunt via the patent ductus arteriosus continues for the first three days of life. The progressive vascular changes described above then begin to occur. By adult life, the pressure needed to propel blood through the lungs is only 20% to 25% of the pressure of systemic circulation.

Dammann [21] next studied 50 cases of pulmonary stenosis in patients over 2 months of age. The findings were essentially those of normal lungs, with the exception of cases with thrombi secondary to polycythemia and those with long-standing dyspnea and secondary emphysema. With defects between the ventricles and the great vessels, or with large patent ductus arteriosus, there is an increased blood flow through the lungs and a pressure in the pulmonary vessels equal in magnitude to the systemic pressure ("common ejectile force"). For this to be possible, the defect (IVSD, PDA, aortic window, etc.) must be at least as great in diameter as the orifice of the aortic valve. Only in this situation are the lungs exposed to systemic pressure, for if the defect is not as large as the aortic orifice, a pressure gradient exists between the two circulations, and, although the pulmonary flow is increased, the pressures are not equalized.

Rushmer [24] described the right ventricle as a distensible bellows or volume pump, with a large surface area able to pump tremendous quantities of blood (up to eight times systemic) through a low-resistance pulmonary bed without a high pressure. The left ventricle, on the other hand, acts as a piston pump against systemic peripheral resistance.

Under the conditions of a common ejectile force, the direction of the flow of blood from the left ventricle will depend upon the respective peripheral vascular resistance of the two circulations. All such patients have pulmonary hypertension of systemic magnitude all of their lives; therefore, the clinical picture presented by such patients is not dependent upon the mere presence of pulmonary hypertension but upon the relative blood flows through the two systems. Blood flow, in turn, is controlled by the resistance offered by the peripheral arterial bed. The systemic vascular resistance is relatively static, but the pulmonary vascular resistance varies during postnatal life according to the evolutionary pattern of the small pulmonary arteries.

Dammann [22] suggests that there are three possible courses that the pulmonary vascular bed may follow after birth in the presence of a common ejectile force.

Phase 1. The pulmonary vasculature follows the normal evolutionary change with decreasing pulmonary vascular resistance, resulting in increased pulmonary blood flow and decreased systemic blood flow. High output failure ensues as the heart works harder in an effort to maintain the systemic circulation.

Phase 2. The fetal state of thick-walled thin-lumened vessels persists, maintaining high pulmonary resistance with balanced flow in the two circulations. The patient may be asymptomatic with minimal or absent cyanosis and no significant heart enlargement.

Phase 3. Secondary intimal changes begin with a gradual increase in pulmonary vascular resistance. The pulmonary pressure eventually exceeds the systemic pressure and a right-to-left shunt occurs. Cyanosis, growth retardation, and dyspnea are seen clinically. The reason that pulmonary vessels develop possibly irreversible intimal changes when exposed to systemic pressures is unknown. There is apparently a difference in the ability of individual patients to withstand such alterations in hemodynamics.

In the progression from Phase 1 to Phase 3, the work of the heart actually decreases,

and cardiac compensation may result. This often leads the family and the physician into a false sense of security.

Dammann [22] studied 87 patients with defects judged to have a "common ejectile force." The microscopic lumen-wall ratios were studied independently from the clinical picture to avoid any prejudice. Those of Phase 1 (high output) occurred in children nearly all under six years of age. Consistently, lumen-wall ratios were greater than in the newborn, but somewhat lower in this group than in normal persons of the same age.

Those of Phase 2 (balanced circulation) ranged in age from 6 to 20 years; all had decreased ratios similar to the fetal type.

Those of Phase 3 were generally older (above six years), were cyanotic, and showed ratios markedly below normal for their own age.

The usual situation was to pass from Phase 1 to Phase 3. However, there were some patients who apparently did not pass through Phase 1 but retained their fetal characteristics and then progressed to Phase 3.

Dammann has postulated that in Phase 1 the infant appears normal at birth and for a short time thereafter. As pulmonary resistance decreases, increased pulmonary blood flow leads to tachypnea, frequent respiratory infections, and possibly high output failure. Some will die at this phase regardless of medical treatment. Some patients survive Phase 1 as the heart grows relatively more than the defect grows, creating a pressure gradient between the two circulations and eliminating the common ejectile force. Those patients who survive progress to Phase 2. The rising pulmonary resistance reduces the extent of pulmonary flow, leading to a balanced circulation. The patient will improve symptomatically. From Phase 2 the usual course is a progression to Phase 3 associated with marked medial thickening and beginning intimal changes. Clinically, these persons become cyanotic. Dyspnea, polycythemia, and right heart failure progress.

The surgical implications of these postulations are obvious, namely, to prevent progression to Phase 3, where irreversible intimal changes have occurred. Optimally, surgery should be done in Phase 1, where the surgical risk is considerably less than later. Surgery in Phase 2 is attended by a high mortality rate, but it may still be followed by a decrease in the medial hypertrophy. Unfortunately, it is often impossible to determine when irreversibility has occurred. The method described by Edwards [25,29] of determining systemic and pulmonary resistance using air and then 100% oxygen may be a valuable means of making this distinction. Various drugs with actions on the autonomic nervous system are being employed by other workers [28,29] in an attempt to determine the flexibility of the pulmonary vascular bed. Dye-dilution curves have also been investigated for this purpose.[14]

Recently, Adams et al.,[20] in a study of children with interventricular septal defect, found a direct correlation between surgical mortality and the degree of pulmonary vascular change noted on lung biopsy. Though intimal change could be found in infants, a tendency to progression was evident with advance in years. Although the risk was high, the presence of minimal intimal proliferation was not necessarily incompatible with a good surgical result.

Summary

Our present understanding of the natural history of congenital heart disease with left-to-right shunts has been brought about by the efforts of many workers. It is clear that the pulmonary vascular bed is the decisive factor in the course of this disease. Initially, increasing pulmonary resistance serves a protective function, but progression of anatomic vascular change may be detrimental to the patient. On this basis, surgery can be justified at an early age to prevent severe pathological pulmonary changes. Major questions which are yet to be answered are by what reliable means we can preoperatively determine the exact

state of diseased vessels which might incur a high surgical risk and what is the course of severe pulmonary vascular change after successful surgical repair.

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Megaloblastic Anemia in Infancy and Childhood in Djakarta

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Since the publications on megaloblastic anemia in infants in 1946 by Zuelzer and Ogden in the United States [1] and by Amato in Italy [2] in 1947, many cases have been added.[3-9] This disease seems to be not uncommon in childhood, especially with malnutrition or kwashiorkor [10,11]; sporadic cases have been described previously by several authors.[12-17]

Inasmuch as the diagnosis of megaloblastic anemia is based on the finding of megaloblasts in the bone marrow, our purpose was to determine the incidence of megaloblastic anemia in children admitted to our pediatric clinic during the last four years on whom bone marrow punctures were done. It was our purpose also to investigate the pathogenesis of megaloblastic anemia and the clinical symptoms in these children.

Materials and Methods

During the years 1954 to 1957, a total of 1,200 bone marrow punctures were done on 800 children for the following indications:

1. Hemoglobin determinations of less than 7.5 gm/100 ml. upon admission or during the hospital stay.

2. A hemolytic syndrome, such as anemia, fever, splenomegaly, jaundice or yellowish appearance, or urobilinogenuria, or a blood picture suggesting a hemolytic anemia (target cells, spherocytes, fragmentocytes, reticulocytes, erythroblastosis, high alkali-resistant or pathologic hemoglobin).

3. A slight anemia in which the blood picture suggested the presence of megaloblastic anemia (megalocytes, megaloblasts, MCV less than 96 cu.μ, MCH less than 32 μg., MCHC less than 30%).

4. Indications of aplastic anemia (anemia with low reticulocyte count, granulocytopenia, thrombocytopenia).

5. Anemia suggestive of a deficiency anemia and which did not react to liver or iron therapy.

6. Anemia of unknown etiology.

7. A clinical and blood picture suggesting the presence of leukemia or leukemia-like disease (anemia, fever of unknown etiology or which did not react to antibiotics, hemorrhagic diathesis, hepatosplenomegaly, adenopathy, granulocytopenia, thrombocytopenia, or the presence of pathologic cells in the blood).

8. Presence of a hemorrhagic diathesis with thrombocytopenia.

9. Severe malnutrition (kwashiorkor).

10. Malignant neoplasias (chloroma, lymphosarcoma, reticulum-cell sarcoma).

In addition, bone marrow punctures were performed on about 100 children with typhoid fever, viral hepatitis, and purulent meningitis.

The methods of hematological examination have been described previously.[7]

Results

Out of 800 children on whom bone marrow biopsies were performed one or more times, 25 children had megaloblasts in the marrow. Five of these children have been described [11] in connection with kwashiorkor and will not be discussed in this paper.

The clinical, blood, and bone marrow data of the remaining 20 cases are recorded in Tables 1, 2, and 3. These children, 9 boys and 11 girls, varied in age from 4 weeks to 6 years and had a body weight far below the normal values for Djakarta children (Fig. 1). Five of these infants were premature infants (Cases 1, 2, 5-7). The diagnosis of megaloblastic anemia was made within a few days after admission in 11 cases (Cases 3, 7, 8, 10, 12-15, 18-20), although the chief complaints were not those caused by anemia. Bone marrow bi-

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TABLE 1.—*Clinical Data*

Case No.	Sex	Age, Wk.	Weight, Kg.	Length, Cm.	Gastric Acidity, Mm. 1.10 N NaOH	Albumin, Gm. %	Urea, Mg. %	Cholesterol, Mg. %	Thymol Turbidity, Units	Bilirubin, Mg. %
1	M	4	1.87		34	3.50	20	106	8.0	0.4
2	F	5	2.05	47			41			
3	F	6	2.80	54	35		30			
4	F	7	2.40	50	46					
5	F	9	1.80	40	4		41			
6	F	9	1.70		27					
7	M	10	3.55	52	1		44			1.0
8	F	10	3.00	47	0	1.75	126	116	8.8	
9	M	26	2.92	57	4	2.02	21	61	6.2	0.4
10	F	30	6.30	65	6	2.82	28	236	29.2	0.8
11	M	34	5.75							
12	F	43	5.04	64		2.93	24	282	9.8	0.9
13	M	52	4.70	70	14	1.89	29	66	17.4	0.4
14	F	52	4.50	62		3.50	30	193	13.8	0.8
15	M	56	5.90	71	16	1.74	31	282	38.2	0.8
16	F	78	4.50	69	8	2.31	32	180	7.4	0.4
17	M	100	8.40	80		2.38	21	72	7.6	0.4
18	M	104	7.70	75	6					
19	F	182	8.20	83	17	1.89	20	68	4.6	1.4
20	M	312	13.40	95		3.04	26	90	4.4	0.6

opsies were performed immediately because of the grave anemia on admission. In the remaining cases, the anemia developed during the hospital stay and bone marrow punctures were done between one week and two months after admission.

The principal diseases in which megaloblastic anemia could develop were malnutrition, prematurity, chronic dyspnea with or without dehydration and toxicosis, and chronic or acute infections, such as meningitis, bronchopneumonia, and otitis media. From the history and by observations in the hospital, it appeared that loss of appetite, loss of weight, fever, and diarrhea were seldom lacking; inadequate feeding at home was encountered in all instances. In Case 7, a premature infant was fed rice water and some bananas after discharge from the hospital, at the age of 2 weeks,

TABLE 2.—*Admission Blood Data*

Case No.	Hgb., Gm. %	Erythrocytes, Millions	Reticulocytes	Normoblasts	Megaloblasts	Megalocytes	Hematocrit	MCV, Cu. μ	MCH $\mu\mu$g.	MCHC, %	Color Index
1	3.1	1.48	47	9,100	+	+	14	95	26	27	0.85
2	2.7	0.96	66	52,600	+	+					0.94
3	3.8	1.28		36,000	+	+					1.00
4	4.5	1.64	9	600	+	+					0.91
5	5.1	1.76	57		—	+					0.96
6	8.0	2.74	27	750	+	+	25	92	30	32	0.98
7	4.0	1.24	27	100	—	+	13	105	32	31	1.07
8	7.1	2.20	9	2,200	+	+					1.07
9	5.5	2.24	85	1,000	—	+	19	80	25	29	0.82
10	6.9	2.10	104	3,600	+	+	20	95	27	30	0.96
11	4.8	2.55	94	600	+	+					
12	4.2	1.44	11	00	—	+	11	76	29	38	0.98
13	4.9	1.68	69	—	—	+	15	90	29	32	0.97
14	1.5	0.61	27	1,200	+	+					0.81
15	3.1	1.08	91	64,000	+	+	10	93	29	31	0.98
16	7.1	2.58	10	50	—	+	27	102	37	28	0.92
17	9.0	3.06	23	—	—	+	28	91	29	32	0.98
18	5.0	1.06	154	800	—	+	18	104	31	29	1.00
19	4.9	1.70	86	120	—	+	19	112	29	26	0.98
20	3.5	1.18	112	1,000	—	+	19	106	29	26	0.99

TABLE 3.—*Bone Marrow Data*

Case No.	Normoblastic					Megaloblastic				Myeloid-Erythroid Ratio	Giant Stab or Meta Cells	Pathologic Megakaryocytes
	Proerythrocytes	Macrocytes	Basophils	Polychromatophils	Acidophils	Promegaloblasts	Basophils	Polychromatophils	Acidophils			
1	1.0	2.0	7.8	31.0	6.4	0	0	0.4	0.4	0.87	+	+
2	0	0	3.8	13.4	11.8	0	0	1.4	1.8	1.42	+	−
3	0.4	1.2	10.2	13.2	10.4	0	0	1.2	1.2	1.32	+	+
4	0	0.2	5.4	3.2	4.2	0	1.8	3.6	9.8	1.86	+	+
5	0.6	1.4	5.4	6.8	14.2	0	0.4	1.6	4.2	1.63	+	−
6	1.6	0.8	2.6	7.8	14.6	0.4	1.4	5.0	11.2	0.95	+	+
7	0	0.4	7.6	22.6	20.4	0	0	0.4	2.6	0.50	+	+
8	0.4	3.8	8.2	11.4	4.2	0.4	7.8	3.4	2.6	1.01	+	+
9	1.4	0.4	8.0	11.0	8.0	0	0.6	0.8	3.4	1.55	+	+
10	0	0	6.4	14.6	7.0	0	0.2	1.0	2.8	1.56	+	+
11	1.4	1.2	3.0	5.0	9.4	0.8	2.8	3.6	9.4	1.16	+	+
12	1.8	0.4	11.6	9.4	12.6	0	0	1.2	0.8	1.01	+	+
13	0.4	0.2	1.6	7.2	9.6	0	0.2	0.8	3.4	2.60	+	+
14	1.4	2.2	1.4	1.6	4.8	1.2	1.6	5.6	15.2	1.34	+	+
15	0	0	6.2	10.4	16.8	0	0	1.2	5.6	0.97	+	++
16	0.6	1.0	2.8	11.6	14.6	0	0	0.2	1.6	1.34	+	−
17	1.0	0.4	3.0	3.6	5.4	−	0.8	3.2	3.0	2.95	+	+
18	1.2	0.6	2.4	6.4	5.0	0	0.6	0.8	2.8	3.13	+++	+
19	0	0.4	4.6	6.2	9.6	0	0	0.8	1.4	1.92	+	+
20	1.4	0	22.4	18.8	4.0	0	0	2.4	0	0.75	+	−

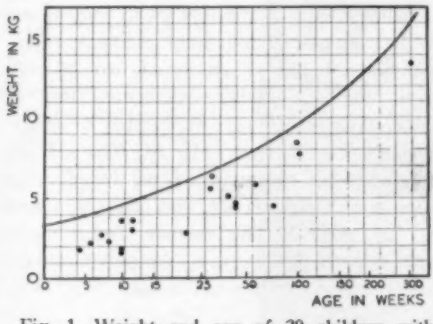

Fig. 1—Weight and age of 20 children with megaloblastic anemia in comparison with the "normal" average weight curve in Djakarta children.

until the second admission, at the age of 10 weeks. Additional feedings, such as vegetables, animal proteins, and vitamins, were not given at all to the older infants or children or were given irregularly in very small quantities. Most of the children were pale and apathetic on admission, and a moderately enlarged spleen and liver were found in about half of the cases. Examination of the gastric fluid in 14 cases revealed a distinctly lowered acidity in 9 instances; with histamine injections these cases showed an increase in gastric acidity.

In general, examination of the serum revealed a low albumin content, normal urea content, low cholesterol, normal bilirubin, and (except in one case) increased values in the thymol turbidity test. In eight cases (Cases 5, 9, 12, 13, 15-17, 19), symptoms of miscellaneous vitamin deficiencies were observed, such as xerosis conjunctivae, Bitot spots, keratomalacia (vitamin A deficiency), areflexia and palpitations (thiamine [vitamin B_1] deficiency), angular stomatitis, and other symptoms indicating vitamin B complex deficiency. In the few cases in which the urine was examined, it appeared saturated with ascorbic acid. True kwashiorkor symptoms, such as edema and hair and skin changes, were not observed.

All of the children showed a very low hemoglobin content of the blood (Table 2) at the time when megaloblasts were found in the bone marrow. The number of red blood cells varied from 610,000 to 3,060,000, and the color index varied between normal values; in five cases (Cases 7, 16, 18-20), the MCV was slightly above normal; the MCH was above normal in Case 6 and less than normal in Case 9. The MCV concentration was normal except in three cases with subnormal values. However, one cannot rely on such values because of their limited validity in grave anemias and be-

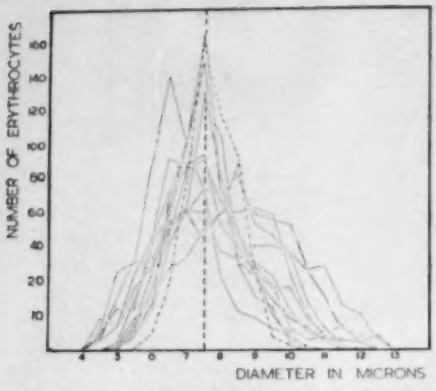

Fig. 2.—Price-Jones curves of the blood smears from children with megaloblastic anemia in comparison with a normal curve (dotted line). Most of these are shifted to the right as well as to the left and show a so-called dimorphic anemia curve, which indicates a dual deficiency of iron and extrinsic factor.

cause one may expect a dual deficiency of iron and liver factors in cases with malnutrition and vitamin deficiencies. In general, the number of the reticulocytes was high (from 8 to 154 per 1,000 red blood cells), indicating an active erythropoiesis.

A constant phenomenon was the appearance of normoblasts, and sometimes of megaloblasts, in the peripheral blood. In two cases, the number of normoblasts was extremely high—52,600 in Case 2 and 36,000 in Case 3. Blood smears revealed megaloblasts in 10 cases (Cases 1-4, 6, 8, 10, 11, 14, 15); megalocytes and anisocytosis in all cases; poikylocytosis in all except Cases 5, 9, 16-19, and polychromacia in all except Cases 5, 17-19. Leukocytosis was a common finding; the number of leukocytes varied from 6,300 to 49,900. Granulocytosis, sometimes with a shift to the left, was regularly seen. The number of the platelets was normal except in four cases (Cases 3, 12, 17, 19). Price-Jones curves of the blood smears revealed a flattening of the tip with a broad base and an extension to the right and to the left. Sometimes a characteristic dimorphic curve in a dual deficiency was observed (Fig. 2). The main cell diameter of the erythrocytes varied between normal values in most cases (above normal in Cases 1, 3, 5, 10, 15; below normal in Case 13).

The bone marrow was characterized by a richness in cells and less fat in comparison with normal bone marrow. The erythropoietic system was active, as can be seen from the low myeloid-erythroid ratio of 2.09 (0.85 to 4.25). The number of megaloblasts varied from 5% to 70% of the total number of nucleated red blood cells; they were characteristic and could be found in all stages. The mature forms were easiest to recognize, i. e., the polychromatic and the acidophilic megaloblasts (Figs. 3-6).

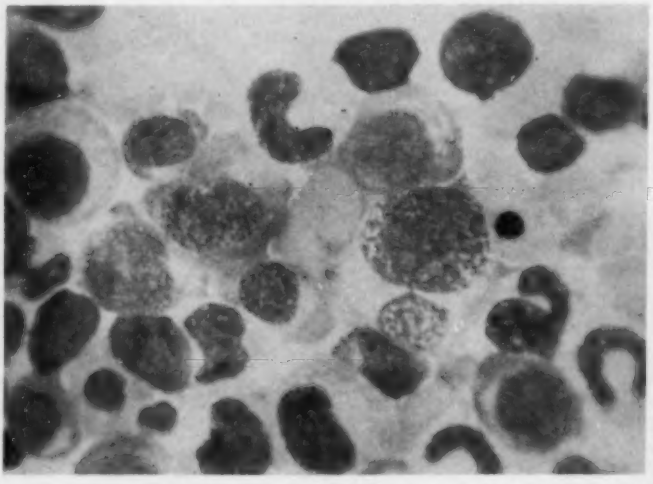

Fig. 3 (Case 14).—A group of acidophilic and polychromatophilic megaloblasts. Note the fine chromatin structure of the nuclei with abundant parachromatin in comparison with a normal acidophilic erythroblast at right. In this case the number of the megaloblasts is much more than that of the erythroblasts.

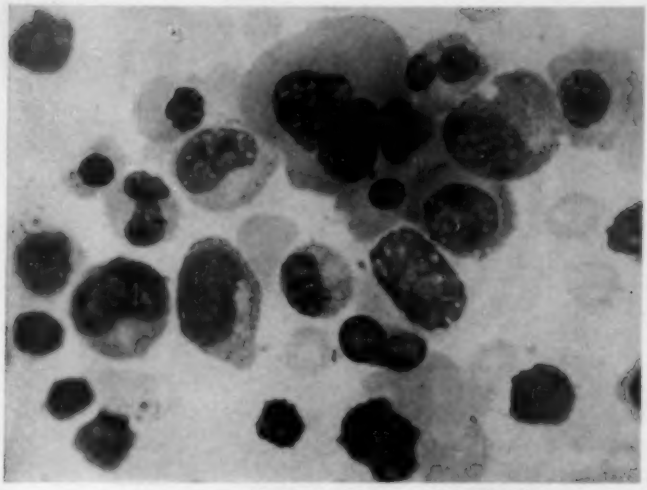

Fig. 4 (Case 17).—A giant acidophilic megaloblast with a double nucleus at the top and some normal acidophilic erythroblasts.

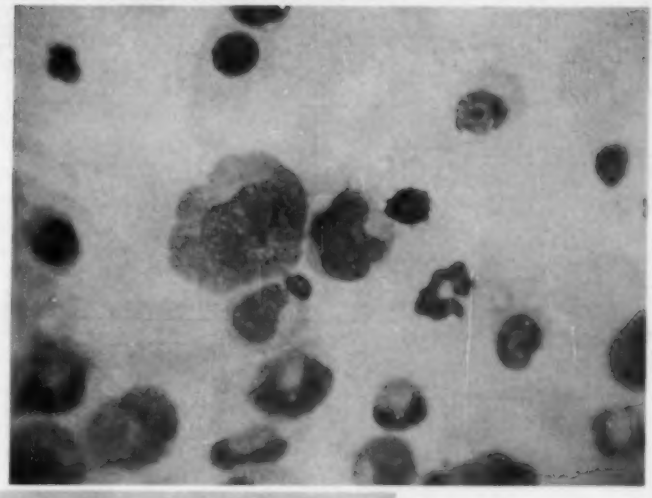

Fig. 5 (Case 11).—A polychromatophilic megaloblast with a typical structure of the nucleus with two distinct nucleoli still present. A normal acidophilic erythroblast at the top.

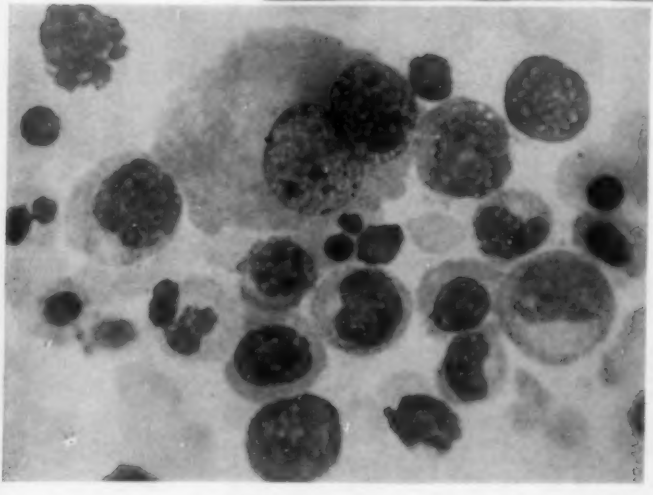

Fig. 6 (Case 11).—A giant polychromatic megaloblast with two typical nuclei still containing nucleoli and other megaloblasts and erythroblasts.

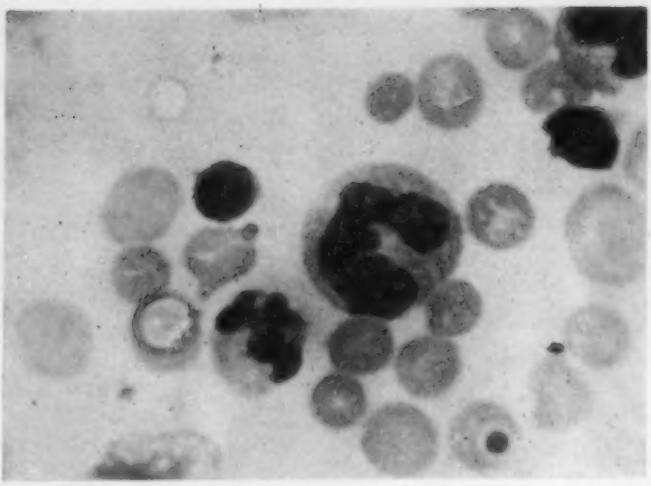

Fig. 7 (Case 17).—Giant stab cell and hypersegmented polynuclear cell. Note the presence of microcytes and macrocytes at the same time.

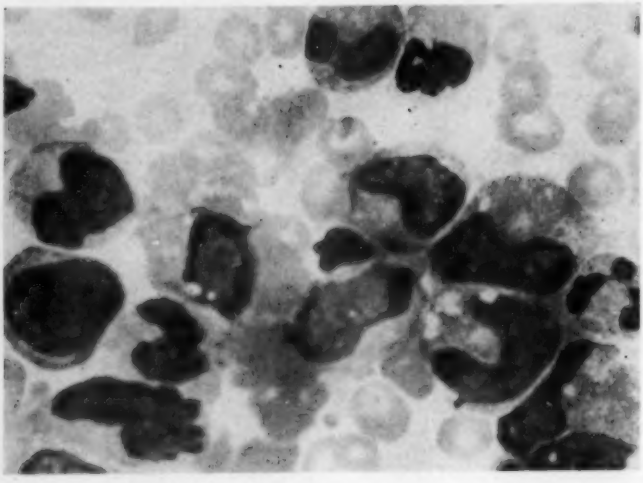

Fig. 8 (Case 16).—A group of giant stab cells and metamyelocytes with vacuolation of the cytoplasm; compare a normal polynuclear cell at right.

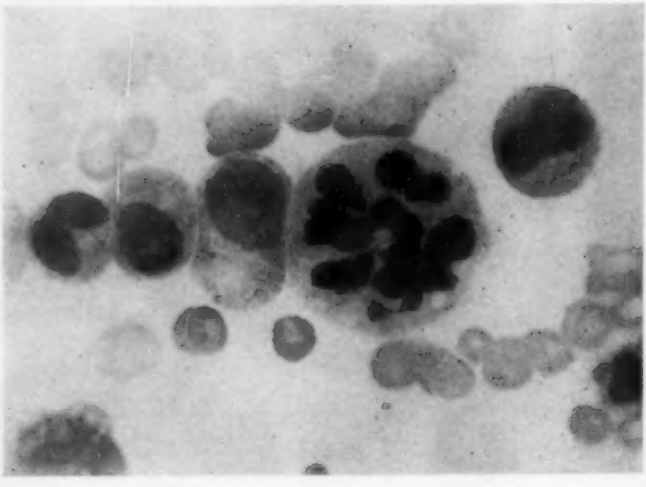

Fig. 9 (Case 20).—A giant hypersegmented polynuclear cell with vacuolation of the cytoplasm. The other cells are normal granulocytes in the bone marrow.

In all cases, giant stab cells or metamyelocytes could be found easily (Fig. 7), and vacuolation of granulocytes (Fig. 8), hypersegmentation of granulocytes (Fig. 9) or megakaryocytes, or multinucleated megakaryocytes were common. The number of megakaryocytes seemed to be normal.

Treatment was based on evaluation of the primary disease. Premature infants were placed in an incubator and managed in accordance with the general regulations. Moderate enteritis was treated only by a regulation of feeding. Enteritis caused by Shigella and by pathogenic coli was treated with oxytetracycline (Terramycin) or tetracycline (Achromycin) and chloramphenicol (Chloromycetin) or streptomycin. Enteritis with dehydration was treated with parenteral fluid therapy with electrolytes; blood transfusion was given to children with grave anemia. Pneumonia, meningitis, and otitis media were treated with antibiotics and, if necessary, by paracentesis. Cortisone was given to infants in dehydration or toxicosis. Vitamin B complex (thiamine 2 mg., riboflavin [lactoflavin] 1 mg., pyridoxine HCl 0.5 mg., Ca pantothenate 3 mg., nicotinamide 25 mg.), and ascorbic acid (vitamin C) 50 mg. were given twice daily as a routine, and 20,000 units vitamin A were administered parenterally on successive days in cases of overt avitaminosis. Megaloblastic anemia was treated with folic acid, 5 to 10 mg. daily by injection, or Eryfol, Roche, 0.5 mg. daily (1 ml. contains 7.5μ of pure cyanocobalamin [vitamin B_{12}] and 5 mg. of folic acid). In every instance folic acid was followed by a reticulocytic crisis. Increase of the hemoglobin was adequate in those cases in which the primary disease could be suppressed, except in Case 16, in which the erythropoietic system of the bone marrow appeared to be hypoplastic. In this case, the hemoglobin content of the blood became normal after two months of hospitalization. Seven children died of the primary diseases for which they were admitted to the hospital (Cases 2, 3, 5, 8, 11, 12, 19).

Comment

The most important criterion for megaloblastic anemia is the presence of megaloblasts in the bone marrow. These cells have in common the fine chromatin structure of the nuclei with abundant parachromatin. In general, the age of the nucleus is younger in comparison with the cytoplasm. The size of the megaloblast is larger than the normal erythroblast of the same age, but this is not a reliable difference. The acidophilic megaloblasts are easier to recognize because of the size of the cell and the broad acidophilic cytoplasm in comparison with a rather young nucleus. The finding of giant stab cells or metamyelocytes and pathologic megakaryocytes are only indicative of megaloblastic anemia and are not pathognomonic because these pathologic cells are commonly found in severe malnutrition or kwashiorkor without megaloblastic anemia. Abnormal mitotic division with a tendency to lobulation and karyorrhexis and changes in the ratio between nucleus and cytoplasm are not typical of megaloblasts but are generally found. A differential diagnosis from pernicious anemia can be made by the finding of free hydrochloric acid in the gastric fluid or by the appearance of this acid after histamine injections. Pernicious anemia in Indonesians is extremely rare.

In reviewing the characteristic findings of the clinical and blood picture in our cases we arrived at the following conclusions:

1. All the children were in a state of malnutrition with a body weight far below normal.

2. All these children, whether born prematurely or at term, had a history of inadequate feeding, with digestive disturbance, diarrhea, chronic enteral or parenteral infections—all conditions in which resorption, utilization, and consumption of the maturating factors for the red blood cells had become deranged.

3. Most of these children had a high grade of anemia, with symptoms of active erythropoiesis (reticulocytosis, polychromasia, erythroblastosis) but no symptoms of

increased red cell destruction (no urobilinogenuria or increase of bilirubin in the blood).

4. Though the finding of anisocytosis with many macrocytes or megalocytes and the distinct acidophilic megaloblasts in the blood smear are pathognomonic for megaloblastic anemia, these were characteristic in only half of our cases.

One would expect an iron deficiency in children with undernutrition and inadequate feeding complicated by disturbances of digestion, utilization, and resorption of the food and by enteral and parenteral infections with increased need for iron to build antibodies. Iron deficiency was present in many of the cases, as may be concluded from the following observations:

1. The finding of hypochromasia and anisocytes in the blood smear with many microcytes next to macrocytes.

2. The relatively low values of MCV and MCHC in many cases.

3. The Price-Jones curves indicating a dual deficiency with a shift of the curve to the left and to the right and the typical two top curves in the so-called dimorphic anemia.[17]

4. The normal mean cell diameter in many cases and less than normal in one case.

5. The response of the anemia to folic acid without blood transfusion was, in our opinion, inadequate in many cases, while, on the other hand, treatment with blood transfusion without folic acid seemed to be adequate; the observations that the serum in iron values in our malnutrition cases were far below the normal.[18]

Hypersegmentation of granulocytes in the blood were not evident in our cases. Leukocytosis with a shift to the left is a reaction to infection and is not a feature usually encountered in megaloblastic anemia.

In general, treatment of our cases consisted of the following procedures:

1. Acute conditions, such as dyspepsia with acidosis, dehydration, and shock, were treated by intravenous drip of a solution consisting of saline and dextrose, acetate, and, later, of blood; the first solution was replaced by lactated potassic saline injection (Darrow's solution), with or without additional cortisone treatment parenterally; after this, dependence was placed on regulation of the diet.

2. Infections were treated with antibiotics.

3. Malnutrition and vitamin deficiencies were treated by adequate food and vitamins.

4. Grave anemias were treated by blood transfusions, megaloblastic anemia, by folic acid with or without cyanocobalamin, and iron deficiency, by

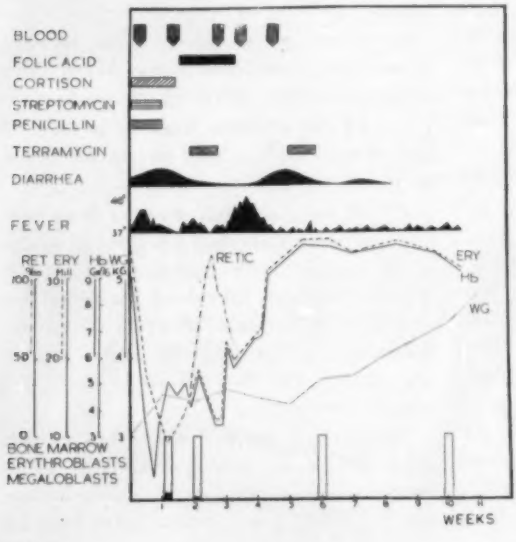

Fig. 10 (Case 7).—The clinical, blood, and bone marrow picture. Folic acid therapy was followed by a reticulocytic crisis, and the condition improved rapidly with antibiotic treatment and blood transfusions. The megaloblasts disappeared within a few days from the bone marrow.

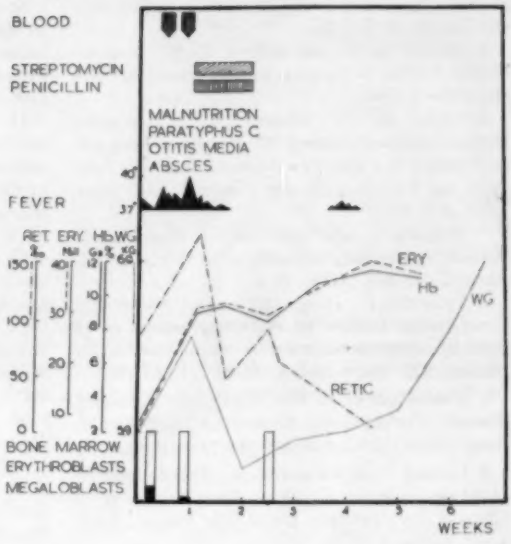

Fig. 11 (Case 15).—A boy with malnutrition and several infections and megaloblastic anemia treated with antibiotics and blood transfusions without folic acid. The condition improved within a few weeks, and the megaloblasts disappeared within two weeks from the bone marrow.

blood transfusion only. Oral iron was contraindicated in most cases because of disturbed digestion. We preferred blood to iron preparations for parenteral use (intravenous or intramuscular).

The mortality was high; eight of the children died because of the grave condition in which they were admitted to the hospital.

Summary

Observations are reported on 20 cases of megaloblastic anemia in premature infants, in infants born at term, and in small children who were admitted to the pediatric clinic of the University of Indonesia in Djakarta during recent years. The body weight of these children was far below normal, and the primary disease for which they were treated in the hospital was not anemia but dyspepsia—with or without dehydration, acidosis, and shock; enteral (pathogenic coli, Shigella, Salmonella) or acute (pneumonia, meningitis, otitis media) infections; prematurity, or malnutrition. Most of these children had miscellaneous iron or vitamin deficiency.

The diagnosis of megaloblastic anemia was based primarily on bone marrow biopsy.

Treatment was based on determination of the primary cause of the disease and consisted of blood transfusion, antibiotics, and folic acid (with or without cyanocobalamin [vitamin B_{12}]). The mortality was high.

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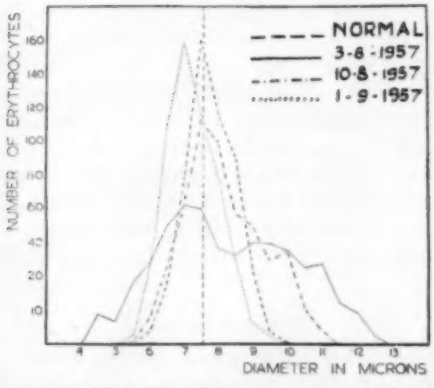

Fig. 12 (Case 15).—Price-Jones curves of blood smears taken at different intervals, compared with a normal curve.

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Eye Injuries in Children

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The purpose of this paper is to call the attention of the general physician to the problems involved in eye injuries in children, to give briefly the generally accepted methods of their management, and to emphasize that the prevention of ocular injury is much more profitable than the treatment.

When compared to all types of injuries sustained by children, eye injuries are not very common. However, the fact that eye injuries are commoner in children than in the general population was shown by a recent study, which revealed that children up to 9 years of age account for over 20% of all the serious eye injuries.[1] Since accidents of various kinds cause about 50% of all blindness in one eye and about 20% of all blindness in both eyes,[2] proper and early treatment and prevention of injuries are extremely important. Because of the delicacy and peculiarities of ocular tissues, an injury that would be insignificant elsewhere is a serious one in the eye and may result in the immediate or eventual total loss of vision in one or both eyes.

To emphasize the significance of how easily a simple dictum is forgotten in handling eye emergencies, the story is apropos of a doctor's little son who received a splash of lime in one eye. The excited mother called the father at his office and was told to rush the child straight to the eye hospital (some 30 minutes away). This was a real emergency, and the father knew it, but he hastily overlooked the one thing that might have saved his son's eye—immediate washing of the eye with copious quantities of water.

Types of Accidents

Sharp objects, blows, falls, and foreign bodies produce the greatest number of the serious eye injuries (82.2% of all major injuries in one analysis [1]). However, BB shot, fireworks,* firearms, explosions (dynamite caps, etc.), chemical burns, and thermal burns are also responsible for many injuries to the eyes.

As was shown by a recent survey, Christmas toys are very significant as a source of severe eye injuries in children.[4] It is surprising how many seemingly harmless toys represent the instrument for severe eye injuries. The more obviously dangerous ones (BB guns, bows and arrows, and darts) are responsible for the greatest number of severe injuries from toys, but sharp-edged metal or plastic toys make a significant contribution also. A harmless rubber-tipped bow and arrow set becomes a dangerous weapon when sticks and reeds are converted to arrows in a friendly game of "cowboys and Indians."

Types of Agents

Injuries to the eyes may be the result of (1) toxic chemical agents, (2) thermal agents, (3) mechanical agents, and (4) certain radiations.

Toxic Chemicals.—Of the toxic chemicals which are likely to be involved in eye injuries in children, household ammonia (10%), lime (CaO, which becomes $Ca(OH)_2$ on contact with moist surfaces), lye (NaOH), and potassium hydroxide (KOH) are the most severely damaging agents. The lime reaction produces a great deal of heat, water is extracted from the tissues, corneal lipids are saponified, and interstitial kera-

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* Injuries to the eye by fireworks have declined in the United States: In 1937, there were 16 patients who lost the vision of one or both eyes and 294 who received less serious eye injuries, while in 1946 the figures were 1 and 44, respectively.[3]

titis ensues. Since NH_4OH enters the anterior chamber in 15 to 30 seconds, KOH and NaOH within 5 minutes and $Ca(OH)_2$ just a little less rapidly, immediate flushing of the eye with water is the one most important measure.[5] Forcing the lids open and holding the eye under a faucet or a low-pressure stream from a garden hose are often handy as well as effective methods. As soon after this as possible, tetracaine (Pontocaine) should be instilled and further irrigation with saline carried out. The lids should be turned and all particles removed with a wet cotton applicator.

In contrast to acid burns, which can usually be evaluated immediately, alkali burns tend to be progressive and may be misleading. Evaluation and treatment by an ophthalmologist are usually necessary but should not take precedence over the *sine qua non* of immediate and thorough irrigation. A new drug, edathamil (Versene), may diminish corneal opacities in some lime burns by removing calcium deposits from the cornea.[6] Prompt and prolonged irrigation of all toxic chemicals from the eye should be done before medical attention is sought or specific treatment begun.

Thermal Agents.—Hot liquids and flaming clothing or kerosene often injure the eyes when the face and upper half of the body are involved in extensive burns, and all too frequently children are the victims of such accidents. Attention to the eyes may be of secondary consideration, owing to the pressing need for life-saving measures. In such instances, Butler[7] has had good results with the use of atropine and antibiotic ointment instillations, and if the eyes had to be incorporated in an over-all head-and-face bandage, he did not dress them again for as long as a week or 10 days. Severe burns should have the attention of an ophthalmologist, but if one is not available at the time of initial care, the above method has proven safe and satisfactory.

Mechanical Agents.—Mechanical agents or foreign bodies may injure the lids and globe in various ways, causing abrasions, lacerations, contusions, and penetrating injuries. The importance of tetanus antitoxin or toxoid should be remembered in all injuries of this type.

Most extraocular foreign bodies may be handled without difficulty. They are to be found most frequently under the upper lid and next most frequently imbedded in the cornea. A moist cotton applicator does not damage corneal epithelium as much as a dry one. Any possibility of intraocular foreign body should be carefully evaluated, and if one is present or suspected, the patient should have the care of a specialist.

If an abrasion is not seen with focal illumination, it may show up after applying to the lower cul-de-sac a fine toothpick cotton applicator of merbromin (Mercurochrome) or fluorescein. The amount of stain thus released is small enough to eliminate the need for irrigating excess stain from the eye.

Lacerations of the lids may require plastic repair, especially if involving a lid margin or canaliculus. It should be remembered that plastic surgery is more easily done at the time of the initial wound before scar tissue has replaced and altered normal anatomical structures, but it should be delayed if other injuries make the patient's condition unsuitable for prolonged anesthesia. Lacerations of the globe should be examined as gently as possible to avoid increasing the damage; both eyes should be patched with sterile dressings, and the patient should be kept on his back until surgical repair can be undertaken.

Contusions produce a variety of eye injuries, such as subconjunctival hemorrhages, mydriasis (the pupil may be permanently dilated), hyphemas, iridocyclitis, traumatic cataracts, vitreous hemorrhages, ruptures of the sclera or choroid, detached retinas, fractures of the orbital bones, especially the orbital rim, and, rarely, avulsion of the optic nerve. Most of these conditions require special care and may be difficult to recognize without careful examination. A

deep anterior chamber may mean a rupture of the sclera in the posterior region.[8]

Penetrating injuries of the lids may also result in injury to the globe, such as a laceration or penetration, and the tactile tension, if soft, should arouse suspicion.

Radiation Agents.—Although eye injuries in children caused by radiation are not common, from watching a welder at work or from exposure to rays from a quartz-vapor sun lamp, they may receive ultraviolet rays sufficient to cause damage. Since the symptoms of severe foreign-body sensation in the eyes do not occur for 6 to 10 hours, the patient may not readily recall having exposed himself. Repeated instillations of butacaine (Butyn) ointment

Fig. 1.—A practical and handy method of quickly irrigating an eye which has been injured with a toxic chemical substance. That there be no delay and that the closest source of water be used are the points to be remembered.

or tetracaine drops may be used to relieve the pain while the corneal epithelium heals —usually within 24 hours. The short infrared rays from electric arcs may rarely produce central retinopathy, as may also visible rays of the sun. This condition is seen most often after an eclipse; the effect is produced by a concentration of rays resulting in a thermal burn of the macula, much like burning a piece of paper by focusing sunlight with a magnifying glass. Tinted glass, glass coated with soot, and photographic film, contrary to popular opinion, do not afford adequate protection for eclipse viewers. The safest way to observe an eclipse is to allow the sunlight to pass through a pinhole in a piece of cardboard and to focus the image on another piece of black cardboard, thus producing a clear image of the sun.[9] By substituting one arm of a pair of field glasses or a small telescope for the pinhole, the spots on the sun can be clearly seen, and the eclipse can be seen more clearly than by viewing through smoked glasses. Before every

Fig. 2.—After every partial eclipse of the sun, numerous persons, especially children, appear with complaints of sudden visual loss noticed during or shortly after the eclipse, which they had watched through dark glasses, exposed photographic film, or pieces of glass smoked with a candle, which do not afford adequate protection.[10]

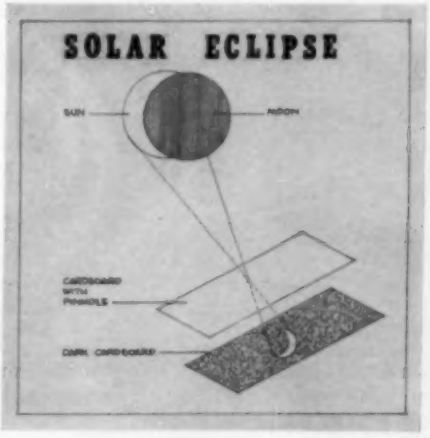

Fig. 3.—A safe way to view a solar eclipse. At least two solar eclipses occur each year in various parts of the world, and each 100 years a total of 237 eclipses occur, of which 84 are partial; 77, annular; 10, annular and total, and 66, total.[11]

eclipse, the potential hazard to the eyes should be widely publicized.

Summary and Conclusions

The importance of the prevention and early emergency care of eye injuries in children is briefly discussed. Stress is laid on the significance of quick and thorough washing of eyes injured by toxic chemicals and upon the importance of protecting an injured eye from further damage before definitive treatment can be instituted. In all cases involving eye injuries visual acuity should in some way be taken and recorded for each eye, and a brief note should be written about how the accident occurred. The delicacy and peculiarities of ocular tissues make the prevention of eye injuries much more profitable than the treatment. In this regard, the dangers of certain toys are emphasized.

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Case Reports

Survival After Neuroblastoma with Widespread Metastasis

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Neuroblastoma is primarily a disease of infants and children. It is not rare, since some 700 cases are reported in the literature. Among the malignancies of children it is probably second only to leukemia.

The features of this disease have been reported in detail by others.[2,8,10,12,14,15,18] The tumor may arise from any part of the sympathetic nervous system, but the usual site is the adrenal gland. The commonest sites of metastasis are the skeleton and the liver, but the concept that skeletal metastasis accompanies a primary left adrenal tumor (Hutchison syndrome) and liver metastasis, a right adrenal tumor (Pepper syndrome), as suggested by Frew,[5] has repeatedly been refuted.[7,8,10,11] The usual presenting sign is progressive enlargement of the upper abdomen caused by the primary tumor, liver metastases, retroperitoneal nodal metastases, ascites or combinations of these. Among the skeletal metastases, those to the skull are most frequent and may be the presenting sign. The patient is usually anemic and febrile. Wilms' tumor and retroperitoneal sarcoma must be differentiated.

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Successful treatment of neuroblastoma has been reported after surgery, radiation, chemotherapy, steroid administration, and various combinations of these modalities.

The prognosis is grave but by no means hopeless; generally, if the patient survives three years without recurrence he can be considered cured. The survival figures in various series reported run from 10% to 31%.[2,4,10,13,16] Metastasis to the skeleton has a poorer prognosis than metastasis to the liver, but long-term survivals may follow in both instances.[1,6,9,13,17]

Spontaneous regression of this tumor and maturation into a well-differentiated benign neoplasm have also been reported.[3,10,17]

It seems worth while to report a six-year survival after rather widespread neuroblastoma in order to emphasize again that this disease is not always hopeless when diffuse metastasis has occurred and that even apparently moribund patients should be treated aggressively.

Report of Case

A white boy, aged 3 months, was admitted through the Free Dispensary to Mercy Hospital on May 20, 1952, because of gradual enlargement of the abdomen for two months. On physical examination, the baby was found to be poorly nourished and there was a large mass occupying the upper two-thirds of the abdomen. The surface was smooth. This mass seemed to be the liver, and it was 10 cm. below the costal margin. Other physical findings were essentially negative. Intravenous pyelograms showed both kidneys to be functioning normally but displaced downward by the mass in the upper abdomen. A barium enema also showed the colon to be displaced downward and anteriorly. Liver biopsy (Silverman needle) was done on May

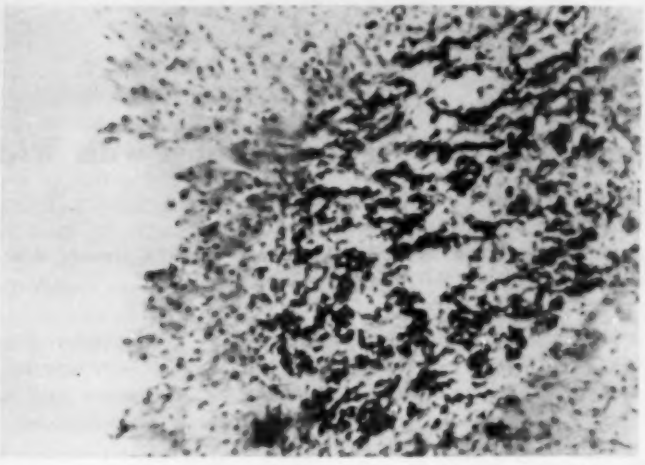

Fig. 1.—Specimen from needle biopsy of liver before any therapy.

24, 1952. The pathologist reported hepatoblastoma (Fig. 1). Roentgen therapy was started on June 3, 1952, with 200 kv., half-value layer 1.5 mm. Cu, at 25 ma. and 50 cm. focal skin distance. The patient was treated through a 10×10 cm. portal to each half of the liver, and a total of 950 r in air was given to each area in 14 days. The patient was discharged from the hospital on June 21, 1952, without change in the size of the abdominal mass. Three weeks later, the patient was readmitted because of fever (102 F), restlessness, and irritability. On examination the abdominal mass occupied almost the entire abdomen to 1 cm. above the inguinal ligament. The general condition of the patient was very poor, and he was considered to be moribund. Nevertheless, he was treated with supportive measures, including blood transfusions, for about one month. When the general condition had improved slightly, another liver biopsy was performed. This time the microscopic diagnosis was probable neuroblastoma, metastatic to the liver (Fig. 2). A second course of x-ray treatment was given from Aug. 11, 1952, to Sept. 3, 1952. The same intensities as above were used, but the portals were directed from posteriorly and laterally to the right adrenal area. The total dose was 1800 r in air from the back and 1600 r in air from the side. When the patient was discharged, on Sept. 10, 1952, the liver was 4 cm. above the umbilicus. By October the liver was only 3 cm. below the costal margin and the baby was gaining weight. In December of the same year the liver was just beneath the costal margin. The patient looked healthy and well nourished, but he was found to have nodularities in the left buttock and right thigh. However, the nodules did not enlarge until

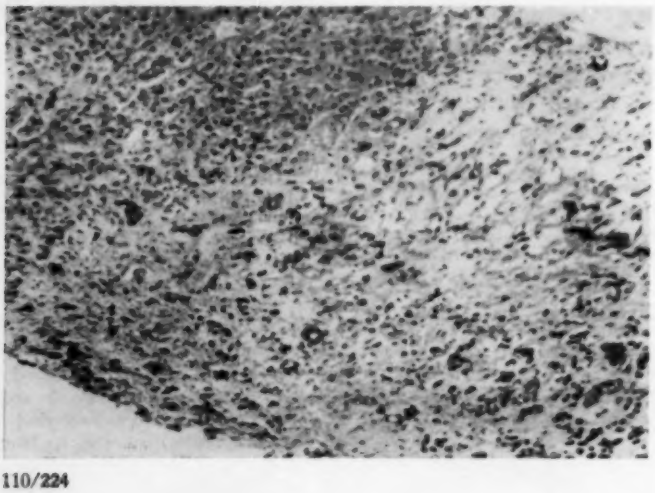

Fig. 2.—Specimen from needle biopsy of liver after first course of x-ray therapy.

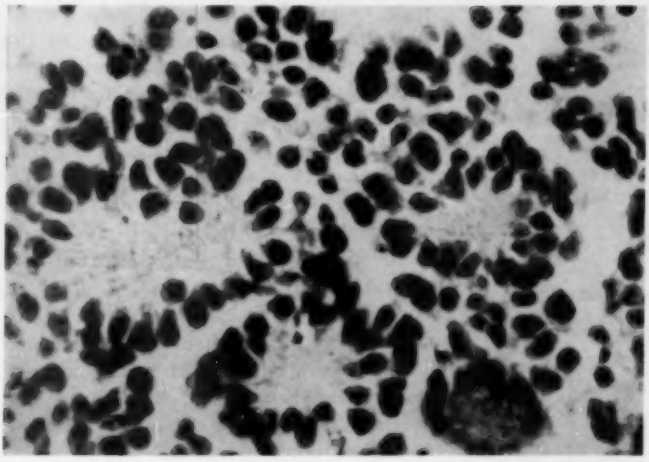

Fig. 3.—Biopsy specimen from thigh.

June, 1953. At that time, the liver became palpable again about 8 cm. below the costal margin and the left inguinal nodes were enlarged. A nodule in the posterior right thigh muscles and a left inguinal lymph node were excised. Both areas proved to be metastatic neuroblastoma (Fig. 3). The mass over the left buttock was much larger and was treated with irradiation (250 kv., half-value layer 2 mm. Cu, and focal skin distance 32 cm., 7.5 cm. circular cone). A single direct portal was used, and a total of 2,400 r in air was given between June 23 and 30, 1953. There was some regression of the mass, but it did not disappear completely despite the higher dose given. On Sept. 2, 1953, the patient was admitted again for excision of the mass in the left buttock. Examination of the specimen again confirmed the diagnosis of neuroblastoma and showed some radiation effect (Fig. 4). At the time of this admission, the liver was no longer palpable and all other previous sites of disease were normal. The patient has been followed regularly to date and has developed normally in stature, with no evidence of recurrent disease up to the time of this report (Fig. 5).

Comment

The primary site of tumor in this case is undetermined, since laparotomy was not performed. We presume it was the right adrenal gland. The presumption is based on the frequency of metastasis to the liver from the right adrenal and the fact that improvement began only after we exposed the patient to irradiation through the pos-

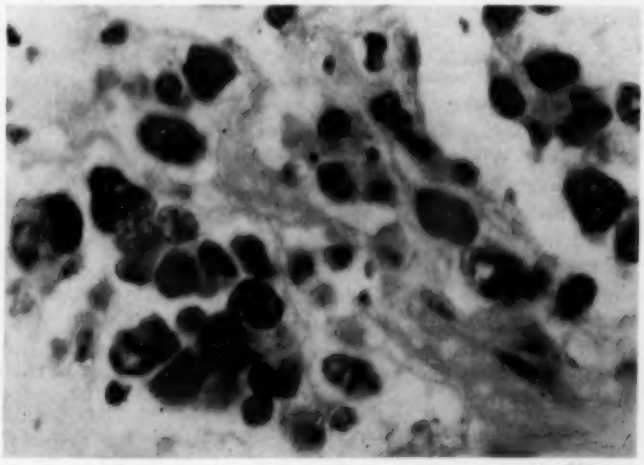

Fig. 4.—Tissue from buttock after x-ray therapy.

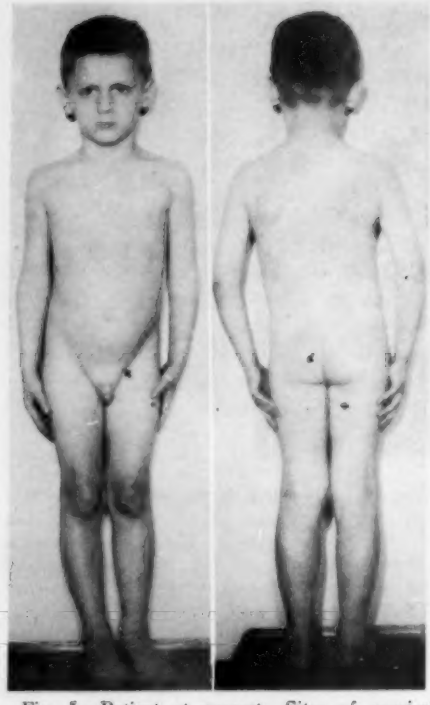

Fig. 5.—Patient at present. Sites of surgical scars marked by arrows.

terior and lateral portals to the right upper quadrant of the abdomen. It has been shown that sometimes regression of visceral and skeletal metastases occur after x-ray therapy is given to the primary adrenal tumor.[6] However, the regression of the liver may also be due to the second course of x-ray therapy, as Wittenborg has suggested giving a second course in treating this kind of malignancy. The dosage we gave in this case falls in the range suggested by Wittenborg,[17] Phillips,[10] and Seaman and Eagleton.[13]

The patient was almost moribund on the second hospital admission, but after x-ray treatment the course slowly changed. As shown in Figures 3 and 4, there is definite evidence of the effect of radiation on the tumor cells. There is no evidence of maturation of the cells into a more differentiated benign form. This suggests that the radiation is primarily responsible for the change in the course of the disease. This apparently confirms what Phillips states about the disease, "if a fatal termination can be prevented during the acutely malignant phase both by sustaining the patient and by full utilization of all available therapeutic agents, the disease may assume a less aggressive and more chronic form and ultimately be brought under control."

The policy of our x-ray department is to treat almost all advanced cases of cancer. Sometimes very gratifying results are obtained. Any increased survival without too much physical discomfort means a great deal to the patient and his family, and occasionally a cure is obtained. This case reconfirms our convictions.

Dr. James H. Peers reviewed the microscopic slides.

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Abstracts from Current Literature

American Heart Journal, St. Louis

Abstracted by F. Kathryn Edwards, M.D.

56, No. 1 (July) 1958

The Value of Aortic and Radial Pressure Pulses in the Diagnosis of Cardiovascular Disorders. J. L. Wright and E. H. Wood.—p. 64.

Electrocardiogram in Chronic Severe Anemia. L. M. Sanghvi, S. N. Misra, K. Bannerji, and K. D. Gupta.—p. 79.

The Circulation in Hyperthyroidism: A Cardiac Catheterization Study Before and After Treatment. S. Humerfelt, O. Müller, and O. Storstein.—p. 87.

* The Relation of the Aortic Root to the Ventricular Septum in Tetralogy of Fallot. Leonard Leight and Lawrence A. Davis.—p. 129.

Complications of Left Heart Catheterization Using the Right Transthoracic Approach. D. Kavanagh-Gray and E. H. Drake.—p. 143.

The Relation of the Aortic Root to the Ventricular Septum in Tetralogy of Fallot.—Angiocardiograms were obtained on three patients who were clinically classical examples of tetralogy of Fallot. The children were cyanotic and ranged in age from 1 month to 9 years. The films were made with use of Elema biplane angiocardiogram apparatus with injection of contrast medium through a catheter tip which was placed in the right ventricle.

The angiocardiograms demonstrate filling of the pulmonary artery and the left ventricle from the right ventricle prior to opacification of the aorta. The authors, therefore, conclude that the usual finding in tetralogy of Fallot is a normal origin of the aortic root.

American Journal of Pathology, Ann Arbor, Mich.

Abstracted by Jay Bernstein, M.D.

34, No. 3 (May-June) 1958

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* Disseminated Lupus Erythematosus, Scleroderma, and Dermatomyositis as Manifestations of Sensitization to DNA-Protein: I. An Immuno-Histochemical Approach. Wadi A. Bardawil, Benjamin L. Toy, Nora Galins, and Theodore B. Bayles.—p. 607.

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* Hyperplastic Infantile Cardiomegaly: A Form of "Idiopathic Hypertrophy" With or Without Endocardial Fibroelastosis, and a Comment on Cardiac "Atrophy." B. Black-Schaffer and M. E. Turner.—p. 745.

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Cellular Lesions in Monkey Kidney Epithelium Induced by Adenoviruses of Simian Origin. J. E. Prier and R. W. LeBeau.—p. 789.

Pathogenesis of Osgood-Schlatter's Disease. Gordon D. LaZerte and Ira H. Rapp.—p. 803.

Disseminated Lupus Erythematosus, Scleroderma, and Dermatomyositis as Manifestations of Sensitization to DNA-Protein: I. An Immuno-Histochemical Approach.—A binding of γ-globulin fractions of serum from patients with disseminated lupus erythematosus, scleroderma, and dermatomyositis with nuclear material in autologous, homologous, and heterologous tissues can be demonstrated with the use of the Coons-Kaplan fluorescent-antibody technique. Enzymatic digestion and blocking procedures indicate that the nuclear

material is deoxyribonucleic acid. Although complement is not required for the reaction, the γ-globulin fraction seems to behave like an antibody. The observations prompt the suggestion that the above-mentioned, "collagen" diseases, and rheumatoid arthritis may be related by varying sensitization to deoxyribonucleic acid proteins and that the "L. E. phenomenon" may be one manifestation of this process.

Hyperplastic Infantile Cardiomegaly: A Form of "Idiopathic Hypertrophy" With or Without Endocardial Fibroelastosis, and a Comment on Cardiac "Atrophy."—By comparing cardiac nuclear density with heart weight, it may be shown that normal heart growth is due to hypertrophy of existing muscle fibers. The same method demonstrated that in five cases of infantile cardiomegaly with endocardial sclerosis there was an increase in the number of cardiac muscle fibers, or a true hyperplasia. The increase could be explained by a single supernumerary generation of myocardial fibers, and the increase in the number of muscle fibers would lead to myocardial inefficiency because of abnormal volume and surface area relationships. The hyperplastic ventricle would respond to increased load by hypertrophy and dilatation as under normal conditions. (The senior author has postulated in a previous paper that endocardial sclerosis is a response to cardiac dilatation.) A corollary of these observations, supported by appropriate data, is that cardiac muscle fibers do not undergo diminution of number in regressive changes and that "cardiac atrophy" is actually "hypocardia."

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Abstracted by D. H. Altman, M.D.

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* Neuroblastoma: A Roentgenologic and Pathologic Study. Owings W. Kincaid, John R. Hodgson, and Malcolm B. Dockerty.—p. 420.

Metastatic Retinoblastoma as a Cause of Diffuse Intracranial Calcification. Lawrence A. Davis and Israel Diamond.—p. 437.

Roentgen Appearances of Lungs in One Thousand Apparently Normal Full-Term Newborn Infants. Jerome Nadelhaft and Kent Ellis.—p. 440.

* Roentgenographic Findings in Hyaline Membrane Disease in Infants Weighing 2,000 Grams and Over. Jerome Nadelhaft and Kent Ellis.—p. 444.

Roentgen Standards for Size of the Pituitary Fossa from Infancy Through Adolescence. Frederick N. Silverman.—p. 451.

The Effect of Prolonged Nutritive Failure on Epiphyseal Fusion in the Human Hand Skeleton. Samuel Dreizen, Richard Snodgrasse, Hamilton Webb-Peploe, and T. D. Spies.—p. 461.

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Lead Poisoning During Infancy and Early Childhood. Paul V. Wooley Jr.—p. 547.

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Radiation Hazards and What Is Being Done About Them: A Symposium; Introduction and Statement of Problem. Edith H. Quimby.—p. 944.

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Practical Suggestions for Reducing Radiation Exposure in Diagnostic Examinations. Lauriston S. Taylor.—p. 983.

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A Summary: Today's Problems in Radiation Hazards and What Is Being Done to Control Them. Richard H. Chamberlain.—p. 1000.

* Hirschsprung's Disease: The Roentgen Diagnosis in Infants. William A. Evans and Robert Willis.—p. 1024.

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* Roentgenographic Features of Neurenteric Cysts. E. B. D. Neuhauser, G. B. C. Harris, and A. Berrett.—p. 235.

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* Roentgenologic Aspects of Benign Chondroblastoma of Bone. George E. Plum and David G. Pugh.—p. 584.
* Mandibulofacial Dysostosis (Treacher Collins Syndrome). Edward J. Pavsek.—p. 598.
Fractures of the Elbow Joint: New Classification and Roentgenologic Guide to Major Pitfalls of Diagnosis and Treatment. Jacob Kulowski.—p. 692.

Hypophosphatasia.—This is a chronic familial disease of uncertain etiology affecting primarily children in whom defective bone formation is associated with low alkaline phosphatase activities in serum and tissues.

This article outlines the major features of the disorder, which was first described by Rathnu, in 1948. Thirty-three cases are summarized in varying degrees of detail, thus giving a very complete picture of this disorder.

The disease picture is somewhat different according to age of onset of findings.

A. Newborns.—Six patients were born at term with a globular and "boneless" skull, soft skeleton, and severe deformities of the extremities. Five of these died within the first few hours of life, and the other died at the 19th day. Three additional infants died between the second and sixth month. They showed irritability, convulsions, failure to gain weight, and slow growth in length. Cyanosis, anorexia, vomiting, constipation, and fever were less common signs. The skeletal deformities were somewhat less severe than the above six, though present from birth.

B. Infants.—In 14 cases symptoms appeared gradually between the first and sixth month of life after a period of apparently good health. The symptoms were those of anorexia, vomiting, constipation, failure to grow, recurrent unexplained fevers, irritability, and hypotonia. Convulsions, cyanosis, and "loud cries" were noted in some. Cranial sutures were separated. The anterior fontanelle was wide, bulging, and often tense, and in most cases there was a rachitic rosary and the ends of the long bones were enlarged. Five patients died between 8 to 10 months of life, and one died at 29 months. Of the surviving eight cases there was some improvement of symptoms noted in all cases followed; however, the skeletal deformities persisted and often became worse. These children walked late and developed genu valgus, and some were short in stature. Craniosynostosis developed in all during the second year of life but caused symptoms in only a few.

C. Children.—Ten children came under observation between the seventeenth month and thirteenth year of life, although mild manifestations could be traced back to early childhood or infancy in a number of these cases.

The usual manifestations were delayed onset of walking, defective gait, knock-knees, painful extremities, marked dental caries with premature loosening and then loss of deciduous teeth, usually incisors; occasionally, short stature, rachitic rosary, and enlarged bone ends were prominent features. Craniosynostosis was seen in only one of these cases. None of these patients died during the period of observation, but at most very slow improvement occurred in children followed.

Laboratory.—No laboratory work was done on newborns who died. Hemograms were normal except in three of the infants, who showed moderate anemia and leukocytosis prior to death.

Serum calcium was elevated in newborns who were investigated, in most of the other infants, and in only three of the older patients. It returned to normal in several.

Serum alkaline phosphatase was decreased in all. Serum phosphorus was normal.

Urinary abnormalities were common in infants and newborns, consisting of albumin, WBC's, and casts and mild to moderate impairment of renal function. These findings were not significant in the childhood group.

Ethanolamine phosphoric acid, an amino acid not present in normal urine, was found in urine of all patients in whom appropriate investigation was made.

Roentgenographically, the basic skeletal abnormalities common to all patients, whether severely or mildly affected, consisted of diminished and irregular bone formation in presence of continuing proliferation of preosseous tissue. Newborns showed changes of marked degree involving the entire skeleton. Many parts were wholly uncalcified, and others showed calcifications of only central portions of bone.

Pathological findings consisted of low-grade nephritis, scarring, and calcific deposits in tubules and peritubular tissues in three of four autopsied cases.

In the bones of newborns the gross pathological picture resembled osteogenesis imperfecta, while in the infant and childhood groups there was a greater resemblance to rickets.

The histology in all cases resembled rickets, but the severity of the changes in all cases was severer than vitamin D deficiency.

Pathogenesis.—There is low phosphatase in serum, bones, and other tissues. The cause of this enzymatic abnormality is not known. No inhibiting agent has been found. It is suggested that this may be congenital and genetically determined.

Since many parents and an occasional normal sib also showed similar serum abnormalities without evidence of bone disease, no simple relationship between these two findings can be considered likely.

Neuroblastoma: A Roentgenologic and Pathologic Study.—The article presents findings on 32 patients encountered at the Mayo Clinic between the 10 years 1945 through 1954.

The term "neuroblastoma" was introduced in 1910, by J. H. Wright, who established the neuroblastic relationship by demonstrating the similar morphology and staining characteristics of these tumors and the cells and fibrils of the sympathetic nervous system.

The average age of the patients was 7.8 years; the median age, 3.5 years. Twenty-one of the thirty-two patients were less than 6 years of age.

The presenting symptoms were commonly abdominal pain, abdominal mass, fever, debility, anorexia, and bone pain. The most frequently encountered finding was an abdominal mass in 69% of cases. Forty-one per cent had peripheral lymphadenopathy, and sixteen per cent showed subcutaneous metastatic nodules.

The primary site was the adrenal medulla in almost 50% of the cases. Other primary sites include the retroperitoneal sympathetic ganglia in the abdomen, the pelvis and thorax, the spinal column, and the cervical sympathetic nerves. Rare primary sites include the small intestine, celiac ganglia, organs of Zuckerkandl, and ganglion nodosum of vagus nerve.

The tumors are locally invasive and tend to metastasize early and widely. In only two of the cases was complete surgical extirpation of primary tumor possible, and both of these were adrenal tumors.

The phenomenon of regression of neuroblastoma to benign ganglioneuroma spontaneously has been reported in the past but did not occur in this series.

Surgical removal is treatment of choice, but, as this can so rarely be accomplished, surgery and irradiation are the usual methods of treatment for local disease.

None of the patients survived more than a year after distant metastases were detected.

The characteristic histologic finding is "rosette formation" and presence of neurofibrils.

Radiographically, demonstration of the mass, which may contain calcium; liver enlargement due to metastases, and displacement of a kidney or ureter are all valuable signs. Primary neuroblastoma of the thorax arises from the paravertebral sympathetic nerves and usually appears as a rounded mass adjacent to the posterior mediastinum.

Metastatic neuroblastoma has a predilection for the skeleton. Forty-four per cent of the cases showed skeletal metastases. Of those with skeletal metastases, multiple involvement was seen in every case but one. In no cases were metastases seen distal to the wrist or ankle. The lesions tended to be bilaterally symmetrical, and generally all of the lesions tend to be of the same type. In 23% purely destructive and in 77% mixed productive and destructive type, productive lesions alone did not occur.

Periosteal reaction was seen in 60% of the cases in which long bones were involved. The appearance of metastatic lesions in the skull is often characteristic, usually consisting of large areas of destruction with irregular indistinct margins. There is frequently associated proliferation of bone. If, in addition, there is "sunburst" type of periosteal proliferation and suture separation due to increased pressure, the diagnosis of neuroblastoma with metastases can be made with relative certainty from the skull examination.

The disease is to be differentiated from Wilms's tumor, lymphoblastoma, leukemia, Ewing's tumor, reticuloendotheliosis, and osteomyelitis and, in the thorax, from benign neurogenic tumors.

Roentgenographic Findings in Hyaline Membrane Disease in Infants Weighing 2,000 Grams and Over.—This article compares the roentgenographic findings in the lungs of seven babies (weighing 2,000 gm. and over) who at necropsy had hyaline-membrane disease with those of normal infants, of infants with other pulmonary diseases, and of infants who recovered from respiratory-distress syndromes.

Histologically the alveoli are characteristically atelectatic and the frequently overdistended alveolar ducts are lined with rather amorphous eosinophilic material. Hyaline membranes are apparently not seen in the lungs of stillborn infants and are rarely found in infants

dying less than two hours after birth. Nearly all deaths occurring due to this condition occur during the first four days after birth. The syndrome is commoner in premature infants and in those delivered by cesarean section.

In all seven cases a generalized marked increase in pulmonary density appeared, consisting of many tiny punctate and some linear densities producing a finely granular or even reticulogranular appearance. In all cases the bronchial air shadows could be seen extending far peripherally into the lungs. In over one-half of the cases peripheral radiolucencies measuring up to 2 mm. in diameter were seen.

These findings were compared with findings in 1,000 newborn infants described in a preceding article by the same authors in this journal. Actually, 59 of these 1,000 full-term babies were in the 2,000 to 2,500 gm. weight group, and they were not significantly different from the remainder of the control group. In none of these normal children did the lung fields or bronchial air shadows appear as described in the cases of hyaline-membrane disease.

Comparison was made with studies of a group of 24 infants with necropsy-proven pulmonary disease other than hyaline-membrane disease, who weighed over 2,000 gm. and who died during the first seven days of life. In none of these 24 cases was there demonstrated that combination of generalized granular density and distinctly defined segmental bronchial air shadows.

Comparison then was made with infants who had recovered from clinical respiratory distress syndromes. Only 3 of these 64 cases showed the radiographic findings described in hyaline-membrane disease. It is suggested that these cases may represent a nonlethal form of the disease.

Hirschsprung's Disease: The Roentgen Diagnosis in Infants.—The diagnostic criteria for diagnosis of Hirschsprung's disease in the newborn and the infant, which are not as well established as they have been in older infants and children, are stressed in this article. The article summarizes 24 cases, 20 in boys and 4 in girls.

In general, the aganglionic segment extends continuously for a varying distance above the anus. Rarely, there may be an isolated zone in which there is an absence of ganglion cells.

An aganglionic rectum may be distended by a Foley catheter or by a large barium enema, but it is characteristically empty of fecal masses. The proximal portion of the aganglionic segment may become dilated by the attempted propulsion of fecal masses from the ganglionic bowel.

The ganglionic bowel, in cases of long standing, is dilated and has a hypertrophied wall, often with an ulcerated mucosa in response to chronic obstruction and retention of feces, the most marked dilatation and hypertrophy occurring immediately above the obstruction. These manifestations are not present in the newborn or during the first few days of life. Thus, the criteria of disparity in caliber between ganglionic and aganglionic segments does not hold in the newborn or young infant.

The Phenomena of Stasis.—A failure of the colon to empty its contents could be recognized in all cases, though not in all examinations, and the value of observing infants for 24 to 48 hours after administration of the barium enema is stressed. Stasis occurs in both the aganglionic and the ganglionic segments but is more marked in the ganglionic segment.

The differential diagnosis in a case presenting disparity in caliber must include rectal web, stenosis, or stricture. The clinical manifestations may be simulated by atresia or stenosis in the small bowel, colon, or rectum or by meconium plug. In these conditions rapid evacuation should occur. Occasionally, in the meconium-plug syndrome, if the plug is not dislodged, stasis of barium would be anticipated. In the case of duplications stasis may occur. In blind-loop syndrome stasis may occur, although this is usually recognized as occurring in the small segment of the small bowel following an enteroenterostomy.

Twenty-four case histories are summarized in brief, but important detail and should be reviewed by anyone interested in this commonly perplexing problem of the newborn or young infant.

Roentgenographic Features of Neurenteric Cysts.—The neurenteric cyst is a cystic structure which has a wall histologically resembling a segment or segments of the foregut. The cyst may have connections by means of a stalk to the meninges and spinal cord through a funnel-like defect in the vertebral bodies.

Four cases are described. Each had the following important findings: a defect in the dorsal vertebral bodies (one case had the defect in both cervical and dorsal vertebral bodies), a mediastinal mass, and displacement of the esophagus by the mass.

The embryological origin is discussed in detail. Bremer has suggested that the neurenteric cyst may result from the partial obliteration of an accessory neurenteric canal.

The neurenteric or chorda canal develops in relation to the formation of the notochord. It passes from the yolk sac, which is destined to form the intestinal tract, through the primitive knot to the amniotic cavity. Hence, this is a communication from the gut to the dorsal surface of the embryo. This is a normal but very short lasting connection, and its final location in the fully developed human is at the tip of the coccyx. Thus, any connection between the intestinal tract and the midline dorsal structures above the coccyx is due to the previous existence of an accessory neurenteric canal.

This theory is used to explain existence of diastematomyelia neurenteric cyst, the giant diverticulum passing from the jejunum through the defect in the right crus of the diaphragm to the posterior mediastinum, midline dorsal dermoid, and anterior spina bifida.

The characteristic roentgen findings are a defect in the anterior aspect of the spine, with faulty formation of the vertebrae and a mediastinal soft-tissue mass. This mass may be continuous with a giant diverticulum or duplication of the intestinal tract and associated with a diaphragmatic hernia.

Roentgenologic Aspects of Benign Chondroblastoma of Bone.—Benign chondroblastoma is a neoplasm of bone which has been frequently mistaken, in the past, for other neoplasms of bone of more serious consequence, notably, chondrosarcoma and giant-cell tumor of bone.

The article reviews 17 cases of benign chondroblastoma from the files of the Mayo Clinic. Ten of the seventeen cases occurred in patients younger than 20 years of age. The site of involvement was the femur in seven cases and the humerus in three cases. The other seven cases were in the pelvis, scapula, or rib.

Physical findings included tumor or joint swelling, limited or painful motion, tenderness or pain on palpation, and muscular atrophy.

The roentgenographic feature of this neoplasm is a central area of bone destruction, which is usually sharply limited from the surrounding normal bone by a thin margin of sclerotic bone. Both trabeculation and periosteal reaction may be seen rarely. In the long bones the tumor usually affects the epiphysis and adjacent shaft.

The differential diagnosis is between benign chondroblastoma, enchondronia, chondromyxoid fibroma, chondrosarcoma, and giant-cell tumor.

Previous lesions, such as metastatic carcinoma, solitary myeloma, or solitary eosinophilic granuloma, which have been curretted or irradiated may resemble benign chondroblastoma.

Treatment of choice is surgical curretage.

Mandibulofacial Dysostosis (Treacher Collins Syndrome).—The mandibulofacial dysostosis syndrome (Treacher-Collins syndrome) is discussed, and one new case is presented.

The findings in this syndrome are as follows: (1) anti-Mongoloid palpebral fissures with coloboma of the outer portion of the eyelid and deficiency of the eyelashes; (2) hypoplasia of the facial bones, especially of the malar bones and mandible; (3) malformation of the external ear and occasionally of the middle and internal ears; (4) macrostomia, high palate (sometimes cleft), abnormal position and malocclusion of the teeth; (5) blind fistulas between the angles of the ears and angles of the mouth; (6) atypical hair growth in the form of a tongue-shaped process of the hairline extending toward the cheeks; (7) additional anomalies, such as facial clefts and skeletal abnormalities.

Thus, using these criteria, cases are classed as complete, incomplete, abortive forms, unilateral forms, or atypical forms. This disorder is well documented with hereditary and familiar occurrence and appears to follow an irregular form of dominant transmission.

The article reviews the embryology of the skull and face as it relates to the production of this disorder.

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Abstracted by Edwin L. Kendig Jr., M.D.

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* Intracranial Calcification Following Tuberculous Meningitis in Children. John Lorber.—p. 38.
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The Titration of Cord Formation as Related to Virulence of Mycobacteria. Irene G. Melvin and H. Mac Vandiviere.—p. 83.
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Effect of Kanamycin on Mycobacterium Tuberculosis in Vitro. R. A. Patnode and P. C. Hudgins.—p. 138.
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The Arcana of Tuberculosis, with a Brief Epidemiologic History of the Disease in the U. S. A.: Parts I and II. E. R. N. Grigg.—p. 151.
* A Simplified Method for Estimation of the Diffusing Capacity of the Lung in Subjects Without Airway Obstruction. M. Henry Williams Jr. and Lenore Zohman.—p. 173.
A Simple Test of Maximal Expiratory Flow for Detecting Ventilatory Obstruction. John R. Goldsmith.—p. 180.
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Relationship of Allergy to Gross Lung Disease and Culturable Bacilli in Tuberculous Mice. David F. Gray and Margaret N. Affleck.—p. 226.
Immunity, Natural Anergy, and Artificial Desensitization in Experimental Tuberculosis. David F. Gray.—p. 235.
Production of Anti-Lung Substances in Rabbits by Homologous Tuberculous Tissue Antigens. Robert G. Burrell and Melvin S. Rheins.—p. 259.

A Rapid Mouse Test for the Diagnosis of Pulmonary Tuberculosis: I. The Enhancement of Experimental Tuberculosis in Mice by Hog Gastric Mucin.—This report attempts to answer four questions:

1. How effective is the intraperitoneal inoculation with mucin in the assessment of the virulence of strains of tubercle bacilli?

2. Does intraperitoneal inoculation with mucin enhance the toxicity of tubercle bacilli?

3. Which organ of the infected mice produced the greatest response following intraperitoneal inoculation of relatively few virulent tubercle bacilli and mucin?

4. What response was given by a large concentration of a virulent strain, as contrasted with a small concentration?

The authors conclude that mucin enhanced experimental tuberculosis in mice. With virulent strains, fewer organisms were required to produce comparable pathologic changes when injected intraperitoneally with mucin rather than with saline. No enhancement of infectivity was obtained with an avirulent strain. Splenic culture produced the most positive results in mice given intraperitoneal injections with H37Rv and mucin and killed. Deaths within 48 hours after inoculation were seen only in the animals given mucin injections.

A Rapid Mouse Test for the Diagnosis of Pulmonary Tuberculosis: II. Preliminary Studies with Patients' Specimens.—In an effort to determine a more rapid diagnostic procedure for the finding of virulent tubercle bacilli in patients' specimens, the authors have reinvestigated a mouse test, previously described by Milzer and Lewis, and adjudged by them to be inferior to either culture or guinea pig inoculation. This test involved the intraperitoneal inoculation of H37Rv or strains derived from patients along with hog gastric mucin.

In the present preliminary report, 46 sputum specimens were obtained from 16 patients who were known to be discharging tubercle bacilli or who were known to have active disease by clinical and roentgenographic evidence. Presence of tubercle bacilli in the sputum of all 16 patients studied was demonstrated in 5 days by the mouse test, whereas culture required 46 days. Of the 46 specimens, 91% were positive for Mycobacterium tuberculosis by the mouse test in 20 days, whereas only 76% were positive by culture in 56 days.

Evaluation of at least 1,000 specimens routinely received in the bacteriology laboratory will be done in order to establish this test on a firm basis.

Intracranial Calcification Following Tuberculous Meningitis in Children.—Calcification of intracranial tuberculous lesions was very rare before the introduction of effective antituberculous drugs.

Routine serial roentgenograms, taken in 130 children who recovered from tuberculous meningitis, revealed pathologic intracranial calcification during life in 63 (48.4%). In two others, who died, intracranial calcification and even ossification were found at necropsy.

Calcification occurred in two main sites: (1) the basal meninges and (2) within the brain substance. The former was by far the commonest, being detected in 49 cases (37%).

The author considers it likely that tuberculous meningitis is becoming the commonest cause of intracranial calcification in children.

A Simplified Method for Estimation of the Diffusion Capacity of the Lung in Subjects Without Airway Obstruction.—The authors describe a simple method of estimating the diffusing capacity of the lung in subjects without airway obstruction. The carbon monoxide uptake is measured, and a value for alveolar carbon monoxide tension is estimated, based either on an assumed normal carbon dioxide tension in the arterial blood or, in persons with evidence of hyperventilation, on an assumed ratio of dead space to tidal volume of 40%. In these studies, the estimated diffusing capacity agreed well with that calculated from the directly measured arterial carbon dioxide tension.

This test may be of value in preoperative evaluation for resectional chest surgery, in determining the diffusing capacity in severely disabled patients, in distinguishing between bronchial asthma and pulmonary emphysema, and in defining pulmonary fibrosis as the cause of shortness of breath in certain patients.

The method is not valid in the presence of greatly elevated arterial carbon dioxide tension, but the commonest cause of this condition, airway obstruction, can be excluded by spirometry. Use of the test is limited to patients with normal or increased alveolar ventilation.

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Abstracted by Werner K. Gottstein, M.D.

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Contribution to the Treatment of Absceding Pneumonia in Infants. G. Bucha.—p. 147.
Contribution to the Entity of Cortical Hyperostosis. Norbert Müller.—p. 155.
On Disorders of Urinary Excretion with Fatal Outcome in Early Childhood. W. Kleint.—p. 165.

Dermatomyositis from the Pediatric Viewpoint.—Until 1954, there were 573 cases collected in the German literature, one-fifth occurring in children under 15 years. More frequent recent publications are not caused by actual increase in occurrence, but by focused attention on collagen diseases. Only three cases observed within 10 years in one of the largest pediatric centers of Germany affirm the rarity of this chronic disease. The local manifestations of skin and muscle, ascertained by biopsy, are not different from those reported in the more recent American publications such as those of Helen Roberts and Louis Brunsting from the Mayo Clinic (*Postgraduate Medicine* 16, 1954) and Ralph Wedgwood (*Pediatrics* 12, 1953). But of interest are the errors of diagnosis on admission and the visceral signs that appear, in our literature, to be commoner in lupus erythematosus. Of further interest is the attempt to find a laboratory test that is, even without biopsy, pathognomonic. In the first case the admitting diagnosis was congenital aortic stenosis; in the second one, nephritis, exudative pleurisy and retinitis, and in the third one, chronic polyarthritis. The treatment was not less frustrating than everywhere else, and therapeutic "success" was often due to the spontaneous remissions that are significant. The fatal intestinal perforation in Case 2 is in accordance with the statement of Wedgwood, who has seen four similar fatal cases resulting from corticosteroids that are apparently always tried without any convincing effect. The systemic reactions, such as anasarca, retinopathy, and electrocardiographic deviations, emphasize the similarity with lupus erythematosus. The German author reports in dermatomyositis an increase of α_2-globulin, electrophoretically determined. Ogryzlo from Toronto has described in lupus erythematosus changes of the L. E. factor of γ-globulins (*Pediatrics* 19:6, 1957). Quite new in this German publication is the evaluation of the creatinine excretion (reduced) that renders the diagnosis possible. If the entity "collagen diseases" will survive the test of time, further studies of the protein metabolism by electrophoresis may improve our knowledge.

Experiences with Cortisone Treatment of Staphylococcic Pneumonia in Infancy and Early Childhood.—From 1955 to 1957, 35 children (out of 47) were treated with cortisone derivatives (besides antibiotics), resulting in a fatality of only 9% and absence of shock symptoms. The authors, working in the pediatric department of the Munich Medical School, proved by paper chromatography an adrenal dysfunction in staphylococcic pneumonia, evidence that justifies the combined antibiotic and corticosteroid treatment.

Archives of Disease in Childhood, London

Abstracted by R. Janet Watson, M.D.

33, No. 167 (Feb.) 1958

Some Physical Measurements in the First Three Years of Life. F. Falkner.—p. 1.
Growth and Development in a Group of Children of Very Low Birth Weight. C. M. Drillien.—p. 10.
The Prognosis of Bronchiectasis in Childhood. A. W. Franklin.—p. 19.
A Consideration of Colostrum and Milk as Sources of Antibodies Which May Be Transferred to the Newborn Baby. K. E. Boorman, B. E. Dodd, and M. Gunther.—p. 24.

The Serum Proteins at Six Months of Age in Infants Fed on Human or Cow's Milk or on Both. F. Hassan and M. Gunther.—p. 30.
The Dietary Treatment of Phenylketonuria. L. I. Woolf, R. Griffiths, A. Moncrieff, S. Coates, and F. Dillistone.—p. 31.
Parathyroid Adenoma in a Child Presenting as Rickets. B. S. B. Wood, W. H. George, and A. W. Robinson.—p. 46.
Acromegaly in a Girl of Eight Years. R. M. Todd.—p. 49.
Malignant Nonchromaffin Paraganglioma of the Thigh. A. MacFarlane and A. R. MacGregor.—p. 55.
Gumma of the Liver in Congenital Syphilis. D. Whitehouse and W. V. MacFarlane.—p. 58.
Paper Electrophoresis of Serum Proteins in Children. W. W. Payne and C. C. Forsyth.—p. 61.
A Clinical and Haemodynamic Study of Ventricular Septal Defect in Infants. G. M. Maxwell, G. G. Rowe, and C. W. Crumpton.—p. 67.
Sweat Analysis in Fibrocystic Disease, Chronic Pulmonary Disease, and Controls. M. M. Weeks and G. A. Brown.—p. 74.
* The Gastro-Oesophageal Region in Infants. G. S. M. Botha.—p. 78.

33, No. 168 (April) 1958

* Regional Obstructive Emphysema in Infancy. J. Thomson and J. O. Forfar.—p. 97.
An Inborn Error of Metabolism with the Urinary Excretion of α-Hydroxy-Butyric Acid and Phenylpyruvic Acid. A. J. Smith and L. B. Strang.—p. 109.
A Case of Hartnup Disease. W. Henderson.—p. 114.
Dissociation as a Guide to Developmental Assessment. R. S. Illingworth.—p. 118.
Dysmaturity. S. Sjöstedt, G. Engleson, and G. Rooth.—p. 123.
Congenital Interruption of the Aortic Arch. B. V. Foley.—p. 131.
Normal Diameter of the Heart in Radiographs of Pre-School Children. D. Hewitt.—p. 134.
The Changing Aetiology of Erythema Nodosum in Children. J. Lorber.—p. 137.
Clinical and Biochemical Changes During Exchange Transfusion. J. W. Farquhar and H. Smith.—p. 142.
Treatment of Persistent Enuresis with the Electric Buzzer. I. G. Wickes.—p. 160.
Recurrent Abdominal Pains: A Field Survey of 1,000 School Children. J. Apley and N. Naish.—p. 165.
Salmonella Meningitis. K. C. Watson.—p. 171.
Calcified Mesenteric Lymphangioma. R. L. Bishton, C. P. Sames, and H. R. E. Wallis.—p. 176.
Sweat Test for the Diagnosis of Fibrocystic Disease of the Pancreas. K. A. Misch and H. M. Holden.—p. 179.

33, No. 169 (June) 1958

ABO Incompatibility and Haemolytic Disease of the Newborn. G. H. Valentine.—p. 185.
* The Disappearance of Foetal Haemoglobin in Congenital Cyanotic Heart Disease. M. Coghlan and M. C. Joseph.—p. 191.
Basophilic Leucocytes in Children in Health and Disease. R. G. Mitchell.—p. 193.
Intraperitoneal Blood Transfusion in Children in Accra with Special Reference to the Treatment of Kwashiorkor. S. B. G. O. Atta.—p. 202.
Traumatic Subperiosteal Haematoma of the Femur in the Newborn. R. G. Mitchell and K. Rhaney.—p. 205.
Subglottic Haemangioma: Two Infants with Laryngeal Stridor. C. A. Holborow.—p. 210.
Intraspinal Neuroblastoma in a Newborn Baby. E. Elefant, V. Vojta, and V. Benes.—p. 212.
Some Unusual Findings in a Family with Friedreich's Ataxia. P. E. Sylvester.—p. 217.
A Case of Intracranial Dermoid Cyst Associated with the Klippel-Feil Deformity and Recurrent Meningitis. A. P. Roberts.—p. 222.
Sirenomelia: Sympus Dipus ("Mermaid"). H. Jolly and E. M. Lamont.—p. 226.
Gargoylism: Clinical, Radiological, and Haematological Features in Two Siblings. S. B. Griffiths and M. Findlay.—p. 229.
Hydranencephaly (Hydrencephaly). L. Crome and P. E. Sylvester.—p. 235.
The Wenckebach Phenomenon and Auricular-Ventricular Dissociation in Children. M. H. Shnier.—p. 246.
A Salt Wasting Syndrome in Infancy. D. B. Cheek and J. W. Perry.—p. 252.
Anorexia and Severe Inanition Associated with a Tumour Involving the Hypothalamus. H. Kagan.—p. 257.
Acute Spinal Epidural Abscess: A Case in an Infant with Recovery. R. G. Rushworth and P. B. Martin.—p. 261.
Cow's Milk Allergy in Infancy. W. Davies.—p. 265.
Frank Beriberi in a Four-Month-Old Infant. T. Giza and J. Armata.—p. 269.
Wm. Heberden's Cases of Anaphylactoid Purpura. A. Rook.—p. 271.

The Gastro-Oesophageal Region in Infants.—This is an exceptionally fine and thorough study of the anatomy of the gastroesophageal region in infants with special reference to the closing mechanism and partial thoracic stomach. The diaphragm, lower esophagus, upper stomach, aorta, and surrounding tissue were removed en bloc from 115 human subjects, fixed in formalin, and carefully dissected. The age ranged from a 32-week fetus to 8 years. The author emphasized that hiatus hernia in adults was a different entity from partial thoracic stomach in infants in that the former was an acquired degenerative process with relaxation of the supporting structures occurring most often late in life. The outstanding features of the anatomy of the gastroesophageal area in childhood were a small powerful hiatus with marked overlap, and oblique lengthy tunnel, a strong phrenoesophageal membrane, and secure fixation of a narrow terminal esophagus. Competence of the closing mechanism of the esophagus is obviously important in infants who are supine most of the time and are fed every

three or four hours. In cases of incompetence of the closing mechanism the author prefers the term "partial thoracic stomach" because of the impossibility in the majority of cases of distinguishing between sliding hiatal hernia and congenital short esophagus, although there is evidence that most cases are due to the latter. The author believes that patients with chalasia are actually suffering from mild degrees of partial thoracic stomach.

Regional Obstructive Emphysema in Infancy.—The authors discuss the mechanism of production of various forms of regional obstructive emphysema and emphasize the susceptibility of the young infant to functional emphysema. They classify emphysema into lobar, lobular, and cystic types, with subgroupings based on pathogenesis. They point out that the newborn infant who may aspirate mucus or amniotic fluid and who is susceptible to respiratory infections is a likely candidate for developing various types of obstructive emphysema. The diagnosis and treatment is also discussed along with 12 illustrative case reports.

The Disappearance of Foetal Haemoglobin in Congenital Cyanotic Heart Disease.—The authors determined the amount of fetal hemoglobin in 25 infants and children aged 6 weeks to 8 years with the tetralogy of Fallot. The cyanosis in most of the patients was severe. Similar studies were done in a control group of 22 in the same age range. Fetal hemoglobin was not found in any child in either group after the age of 7½ months, and the rate of fall in infancy was the same in both the cyanotic and the control group.

Blood, New York

Abstracted by Audrey K. Brown, M.D.

12, No. 12 (Dec.) 1957

An Unusual Syndrome of Hemolytic Anemia, Thrombocytopenic Purpura and Renal Disease. Clare N. Shumway Jr. and Gerald Miller.—p. 1045.

* Alkali Resistant Type of Hemoglobin in Women with Molar Pregnancy. Yehuda M. Bromberg, Maccabi Salzberger, and Abraham Abrahamov.—p. 1122.

Preparing Standard Solutions of Cyanmethemoglobin. William H. Crosby and Donald N. Houchin.—p. 1132.

Alkali Resistant Type of Hemoglobin in Women with Molar Pregnancy.—In the second or third trimester of pregnancy the finding of significantly high blood levels of fetal hemoglobin has been considered by some to be due to excessive production of fetal hemoglobin by the mother's "embryonic" hematopoietic system reactivated by hormonal or other factors in pregnancy.

Four cases of molar pregnancy were studied in which there was also production of large amounts of chorionic gonadotropin. Fetal hemoglobin values were determined at weekly intervals before and after evacuation of the hydatiform mole. In these four patients with molar pregnancy the fetal hemoglobin concentration was found to be significantly higher than that found in control groups of normal early pregnancy and in imminent and incomplete abortion. After molar abortion fetal hemoglobin decreased gradually, reaching normal values within three to five months.

It is felt that the increased production of fetal hemoglobin in these patients may be due to reactivation of the mother's "fetal" erythropoietic activity by an unknown mechanism.

13, No. 1 (Jan.) 1958

Absorption of Iron as a Problem in Human Physiology: A Critical Review. Hugh W. Josephs.—p. 1.

Studies on Erythropoiesis: Part V. The Effect of Cobalt on the Production of Erythropoietin. Eugene Goldwasser, Leon O. Jacobson, Walter Fried, and Louis F. Plzak.—p. 55.

* The Diagnosis of Thalassemia Trait by Starch Block Electrophoresis of the Hemoglobin. Park S. Gerald and Louis K. Diamond.—p. 61.

13, No. 2 (Feb.) 1958

* The Hemoglobin D. Syndrome. Amoz I. Chernoff.—p. 116.

The Effects of Acute Protein Depletion on the Distribution of Radioiron in Rat Tissues. W. F. Bethard, R. W. Wissler, J. S. Thompson, M. A. Schroeder, and M. J. Robson.—p. 146.

The Diagnosis of Thalassemia Trait by Starch Block Electrophoresis of the Hemoglobin.—Until Kunkel and Wallenius observed a characteristic alteration in the hemoglobin electrophoretic pattern of thalassemia heterozygotes, a suitable diagnostic test for thalassemia minor was not available. Using starch-block electrophoresis, they demonstrated that a minor component of the hemoglobin in normal persons could be separated from the major

portion. In patients with thalassemia minor this small fraction with E-like mobility (designated the A_2 component) was found to be significantly increased above normal values.

In the present report, a group of 23 adults, parents of children with thalassemia major, were studied with use of the starch-block electrophoresis as well as more conventional hematologic hemoglobin measurements. Since thalassemia major is thought to be the result of homozygosity for the thalassemia gene, this group of parents was thought to constitute a population heterozygous for thalassemia.

The A_2 levels in this group were elevated and ranged from 3.3% to 6.8%, with a discontinuous distribution, a gap occurring between 3.8% to 4.4%. Such a distribution suggests genetic factors, and analysis of six thalassemia-trait pedigrees indicated that the A_2 value in affected members was very similar within individual pedigrees.

In the group representing the heterozygous state for the thalassemia gene there was invariably reduced mean cell volume (microcytosis) and increase in the A_2 fraction of hemoglobin, and the authors conclude that diagnosis of thalassemia trait should be limited to those cases which fulfill these minimum diagnostic criteria.

The Hemoglobin D Syndrome.—An incidence of hemoglobin D among American Negroes of 0.4% is reported, and some of the clinical, hematologic, and genetic characteristics of hemoglobin D trait and homozygous hemoglobin D disease are described. No hematologic abnormality was defined for the hemoglobin D trait, except that by electrophoresis hemoglobin D, as well as hemoglobin A, was detectable.

Homozygous hemoglobin D disease is described in a 40-year-old Negro woman who had only a mild hemolytic disorder. The red cells were microcytic and normochromic, and there were many target cells on stained blood film. Hemoglobin levels were normal or low normal. The electrophoretic mobility of hemoglobin D is like that of hemoglobin S, but gelling, tactoid formation, and sickling are not found. The solubility of hemoglobin D in 2.53 M phosphate is also higher, and this distinguishes it from hemoglobin S.

Hemoglobin D disease is apparently much less of a problem than any of the previously described pure hemoglobinopathies.

It should be noted that specific proof of homozygosity for hemoglobin D was lacking in this case, as the patient's parents were dead. The evidence presented is strongly suggestive, since hemoglobin D was present in four siblings in this family. However, the combination of thalassemia with hemoglobin D could manifest as 100% hemoglobin D.

Boletín Médico del Hospital Infantil, México, D. F.

Abstracted by Mary Allen, M.D.

15, No. 2 (April) 1958

The Department of Pathology and the Hospital Infantil of Mexico, Editorial. Lazaro Benavides.—p. 145.
Some Data Regarding the Historical Development of the Concept of Pathology. Maximiliano Salas.—p. 147.
° The Pathology of Hyaline Membrane (An Analysis of Sixteen Cases and the Revision of Some Concepts of This Disease). Maximiliano Salas.—p. 151.
Morphological Study of Renal Changes in Glomerulonephritis and in the Nephrotic Syndrome in Children. Kurt Ambrosius and Higinio Esparza.—p. 171.
Pathology of Amebiesis in an Analysis of Forty-Four Cases in Children. Maximiliano Salas, Octavio Angulo, and Higinio Esparza.—p. 185.
Pathology of Poliomyelitis in Children. Maximiliano Salas, Octavio Angulo, and Jesus Villegas.—p. 223.
Pathology of Generalized Tuberculosis in Children: An Analysis of One Hundred Twenty-Five Cases and Revisions of Some Concepts of This Disease. Maximiliano Salas, Armando Ricalde Gamboa, and Carlos Fuente Olano.—p. 251.
Pathology of Tuberculosis Meningitis. Maximiliano Salas, Octavio Angulo, and Guestavo Lopez.—p. 285.
Pathology of Osteo-Articular Tuberculosis in Children: An Analysis of One Hundred Thirty-Four Cases. Maximiliano Salas, Octavio Angulo, and Jesus Villegas.—p. 311.

The Pathology of Hyaline Membrane (An Analysis of Sixteen Cases and the Revision of Some Concepts of This Disease).—The author reviewed the bibliography of hyaline-membrane disease, giving some statistics and reminding us that the hyaline membrane is never found in stillborn infants and rarely in infants who live more than five days.

Of the 16 cases studied 2 were in patients born as one of triplets and 2, in patients born as one of twins. Twelve patients were born prematurely, and with 11, labor was prolonged.

In all cases but one, breathing was spontaneous. The labored breathing began from ½ to 96 hours after birth. The duration of life after the onset of the respiratory distress was from 4½ to 96 hours. Bronchopneumonia was a complication in seven instances.

Clinical symptoms always include dyspnea and cyanosis. Retraction of thoracic walls was described in all 16 infants, but sternal retraction was observed in only nine.

Diffuse infiltration was seen in the films of all six patients who were x-rayed.

Subnormal temperatures were found in 12 cases and high fever in 2.

Hyaline membrane was given as the cause of death nine times and hyaline membrane and bronchopneumonia seven times, but abundant hyaline membrane was found in cases diagnosed as bronchopneumonia.

There were also some areas of massive atelectasis, diffuse congestion, and focal emphysema in some cases.

The extrapulmonary lesions found are interesting. There were subarachnoid hemorrhages in eight cases and hematomata of the scalp in five. In one infant there was hemorrhage into the peritoneum and in one case a hemorrhage beneath the capsule of the liver.

There was histological evidence of immaturity in the kidney and liver in 15 cases. A smaller number of cases showed thyroid, intestinal cerebellar, and pancreatic immaturity. The pancreas showed a fetal type of tissue in one case only.

Bacteriological studies of pulmonary tissue showed the presence of Klebsulla pneumoniae in three cases. Micrococcus pyogenes var. aureus was found in two cases and Proteus vulgaris with Escherichia coli, in one case. Tetrangenous Gafkya was found in one case. Unfortunately bacteriological studies were not completed in all cases.

Comment: The entire issue is devoted to pathology, and there are some excellent photographic illustrations of sections and also of x-rays.

Canadian Medical Association Journal, Montreal

Abstracted by H. M. Keith, M.D.

78, No. 12 (June 15) 1958

Tetanus Neonatorum. Maureen H. Roberts.—p. 922.

Exchange Transfusion in the Newborn Using Heparinized Blood. G. H. Valentine.—p. 927.

* Vitamin B_6 in Mental Deficiency: Xanthurenic Acid Excretion in Phenylketonurics. B. Tischler and E. G. McGeer.—p. 954.

Vitamin B_6 in Mental Deficiency: Xanthurenic Acid Excretion in Phenylketonurics.—Studies on animals indicated that vitamin B_6 plays an important role in transamination reactions. In phenylketonurics there is probably a constant demand for vitamin B_6 in the transamination of phenylalanine to phenylpyuric acid. It is known that vitamin B_6 is essential for tryptophan metabolism. When this is deficient, xanthuremic acid is excreted in the urine. The latter is used as a test of vitamin B_6 deficiency.

Seven patients with phenylketonuria and six controls were studied for xanthuremic acid excretion before and after a tryptophan load. There was no significant difference in the two groups. It appears unlikely that phenylketonurics on an adequate diet will be deficient in vitamin B_6.

79, No. 1 (July 1) 1958

Infantile Cortical Hyperostosis: Report of A Case in an Indian Infant. Cameron Corrigan and R. B. Lynn. —p. 41.

* A Winter Epidemic of Poliomyelitis in Saint-Augustin, Que.: III. Laboratory Studies. V. Pavilanis and A. Frappier.—p. 11.

A Winter Epidemic of Poliomyelitis in Saint-Augustin, Que.: III. Laboratory Studies. In January, 1950, an epidemic of poliomyelitis occurred in an isolated Quebec village. The mean temperature at the time was 0 F. At a party 2 children became paralyzed suddenly (fatigue?), and in the following week 7 more became paralyzed and 14 presented meningeal signs.

Virus studies showed that during the epidemic 90% of the population harboured Type 1 poliomyelitis virus.

Two years after the epidemic almost 100% of the population had Type 1 polio antibodies in their blood. Only children born after the epidemic had Type 1 poliomyelitis antibodies to a smaller degree.

From the serological epidemiology it was possible to prove that 11 years previous to the Type 1 epidemic there had been another Type 2 poliomyelitis epidemic. This epidemic left not only a high level of Type 2 polio antibodies but also a resistance to Type 1 poliovirus.

Journal of Clinical Endocrinology and Metabolism, Springfield, Ill.

Abstracted by Judson J. Van Wyk, M.D.

18, No. 2 (Feb.) 1958

° Adrenocortical Insufficiency with Normal Basal Levels of Urinary 17-OHCS: Diagnostic Implications. N. Abu Haydar, J. R. St. Marc, W. J. Reddy, J. C. Laidlaw, and G. W. Thorn.—p. 121-133.

Treatment of Cushing's Syndrome with Amphenone: Report of Two Cases, One with Probable Thymoma. E. P. McCullagh and H. A. Tretbar.—p. 134.

° Estimation of Growth Hormone Content in a Single Human Pituitary. C. A. Gemzell and C. H. Li—p. 149.

° Peptide-Linked Iodotyrosines and Iodothyronines in Blood of a Patient with Congenital Goiter. L. J. DeGroot, S. Postel, J. Litvak, and J. B. Stanbury.—p. 158.

Metabolism of Free and Conjugated 17-OHCS in Thyroid Disease. H. Brown, E. Englert Jr., and S. Wallach. —p. 167.

Serum Inorganic Phosphorus Levels in Eunuchism and in Feebleminded States. J. B. Hamilton and L. D. Bunch.—p. 180.

Studies of Adrenal Corticosteroids: I. Estimation of Plasma Corticosterone and Cortisol. R. S. Ely, E. R. Huges, and V. C. Kelley.—p. 190.

Studies on the Origin of Aldosterone During Human Pregnancy. J. C. Laidlaw, M. Cohen, and A. G. Gornall.—p. 222.

Ovogonia in Rudimentary Gonads in a Case of Turner's Syndrome with Male Sex Chromatin Pattern. R. B. Greenblatt.—p. 227.

18, No. 3 (March) 1958

° Hypocalcemic Hypercalciuria During Vitamin D and Dihydrotachysterol Therapy of Hypoparathyroidism. J. Litvak, M. P. Moldawer, A. P. Forbes, and P. H. Henneman.—p. 246.

A Paper Chromatographic Method for the Measurement of Pregnanediol in Urine. W. R. Eberlein, and A. M. Bongiovanni.—p. 300.

Adrenocortical Carcinoma Causing Feminization in an Adult Male. E. T. Wolf, L. C. Mills, B. L. Newton, L. L. D. Tuttle, R. A. Hettig, V. P. Collins, and W. B. Gordon.—p. 310.

° A Case of Feminizing Adrenal Tumor in a Girl. A. H. Snaith.—p. 318.

"Primary Aldosteronism" Associated with Significant Edema. R. S. Goldsmith, F. C. Bartter, P. J. Rosch, W. H. Meroney, and E. G. Herndon Jr.—p. 323.

Plasma Level of 17-OHCS in Umbilical Cord Blood: A. Umbilicalis vs. V. Umbilicalis. H. Kawahara.—p. 325.

Somatic Sex of Anencephalic Infants. E. V. Perrin, and K. Benirschke.—p. 329.

18, No. 4 (April) 1958

Two Naturally Occurring Metabolites of Progesterone: Isolation, Identification, Biologic Activity, and Concentration in Human Tissues. J. Zanders, T. R. Forbes, A. M. von Munstermann, and R. Neher.—p. 337.

I^{131} Metabolism in Thyroid Slices of Patients with Various Thyroidal Disorders. O. P. Schumacher, F. R. Keating, and A. Albert.—p. 354.

Effect of Iodide on the Release of Thyroid Hormone in Hyperthyroidism. R. Goldsmith, C. Herbert, and G. Lutsch.—p. 367.

Olfactory Perception Thresholds in Hypogonadal Women: Changes Accompanying Administration of Androgen and Estrogen. R. A. Schneider, J. P. Costiloe, R. P. Howard, and S. Wolf.—p. 379.

Urinary Corticosteroid Patterns in Patients with Adrenocortical Dysfunction. I. Dyrenfurth, S. Sybulski, V. Notchev, J. C. Beck, and E. H. Venning.—p. 391.

Effect of Prednisone on Adrenal Responsiveness to ACTH in Normal Subjects and in Patients with Cushing's Syndrome. J. Geller, A. S. Alvarez, A. Gutman, A. de Freitas, J. L. Gabrilove, and L. J. Soffer.—p. 409.

18, No. 5 (May) 1958

Hypophysectomy During Pregnancy in a Patient with Cancer of the Breast. B. Little, O. W. Smith, A. G. Jessiman, H. A. Selenkow, W. van't Hoff, J. M. Eglin, and F. D. Moore.—p. 425.

° Levels of 17-OHCS in Maternal and Cord Plasma in Anencephaly. J. Nichols, O. L. Lescure, and C. J. Migeon.—p. 444.

Day-to-Day Fluctuation in Excretion of Human Pituitary Gonadotropin. A. Albert, S. Kelly, L. Silver, J. Kobi, and L. Bloodsworth.—p. 453.

Excretion of ICSH by Normal Males and Females of Various Ages. J. W. McArthur, F. M. Ingersoll, and J. Worcester.—p. 460.

Cerebrospinal Fluid Proteins in Myxedema. D. Bronsky, H. Shrifter, J. De la Huerga, A. Dubin, and S. S. Waldstein.—p. 470.

Metabolic Observations in Thyrotoxicosis with Hypercalcemia. C. R. Kleeman, S. Tuttle, and S. H. Bassett.—p. 477.

Severe Uterine Bleeding and Degenerative Skeletal-Muscle Changes in Unrecognized Myxedema. G. T. Ross, D. A. Scholz, E. H. Lambert, and J. E. Geraci.—p. 492.

Studies on Pathogenesis of the Anemia of Hypothyroidism. R. Buso, S. T. Olavarrieta, and R. M. Suarez.—p. 501.

Effect of Triiodothyronine on Serum Lipids and Lipoproteins of Euthyroid and Hyperthyroid Subjects. D. A. Sachs, E. Danielson, M. C. Isaacs, and R. E. Weston.—p. 506.

Biologic Half-Life of I^{131} in Thyroid of Healthy Males. G. Rosenberg.—p. 516.
Comparison of 17-Ketogenic (Norymberski), Glenn-Nelson, and Reddy Methods for Determination of C_{21} Urinary Steroids. O. J. Golub, C. Sobel, and R. J. Henry.—p. 522.
Metabolic Insufficiency, Editorial. F. R. Keating Jr.—p. 531.
Half-Life of Radiothyroxine in Non-Thyroidal Hypometabolism. N. B. Lasker and R. J. Ryan.—p. 538.
Contribution to the Study of Adrenocortical Secretory Function in Thyrotoxicosis. L. Mikulaz and S. Nemeth.—p. 539.
Method for Demonstrating Increased Inactivation of Pitressin in Diabetes Insipidus. J. Hankins.—p. 543.

Adrenocortical Insufficiency with Normal Basal Levels of Urinary 17-OHCS: Diagnostic Implications.—Seven patients are described who had increasing pigmentation of the skin and some other symptoms of Addison's disease but normal basal levels of 17-hydroxycorticoids in the urine. None of the patients responded to the intravenous administration of corticotropin (ACTH) by a rise in steroid excretion, thus demonstrating the absence of any significant adrenocortical reserve. Included in the series is a 2-year-old white girl who was admitted because of episodes of loss of consciousness and convulsions associated with hypoglycemia.

Estimation of Growth Hormone Content in a Single Human Pituitary.—Growth hormone was purified from a pool of 10 human pituitaries obtained at autopsy and singly from 11 individual pituitaries. The purification technique utilized a chromatographic procedure, and the hormonal content was estimated by zone electrophoresis and biological assay in hypophysectomized rats. The amount of growth hormone found ranged between 3 and 6 mg. per pituitary, but no data are given on the ages of the patient studied.

Comment: As yet there are no data on the changes in growth hormone secretion with age or the precise role of growth hormone in determining the human growth curve. Although the present technique is perhaps insufficiently refined for this purpose, it may be expected that this important information will not be long in coming.

Peptide-Linked Iodotyrosines and Iodothyronines in Blood of a Patient with Congenital Goiter.—A 28-year-old white woman is reported who developed signs of hypothyroidism in infancy and a goiter at age 8. When she was studied, she had a PBI of 2μg/100 ml. and a 24-hour iodine uptake of 57%. None of the usual types of defect in thyroid synthesis associated with metabolic cretinism could be demonstrated. It was found that she released large quantities of an abnormal metabolically inactive iodinated protein into the blood stream. This protein had the mobility of albumin and may have been derived from thyroglobulin.

Hypocalcemic Hypercalciuria During Vitamin D and Dihydrotachysterol Therapy of Hypoparathyroidism.—Hypercalciuria was found in 10 patients with postoperative and idiopathic hypoparathyroidism at a time when there were low fasting serum calcium levels. A direct effect of vitamin D and dihydrotachysterol in decreasing tubular reabsorption of calcium is postulated as the most likely cause. In view of these findings, the Sulkowitch test cannot be regarded as a reliable guide to the therapy of hypoparathyroidism.

A Case of Feminizing Adrenal Tumor in a Girl.—A girl of 5½ years presented the classical picture of isosexual precocity, including menstrual bleeding, breast development, and a bone age of 12 years. No signs of virilization or Cushing's syndrome were present. The only clue to the presence of an adrenal neoplasm was a 17-ketosteroid level of 17-20 mg/24 hr. The tumor was removed *in toto*, and following surgery the signs of precocious puberty subsided and the 17-ketosteroids fell to normal values.

Levels of 17-OHCS in Maternal and Cord Plasma in Anencephaly.—Plasma for steroid determinations was obtained from the mother and from the umbilical cord in five cases of anencephaly. All of the infants died at birth, and autopsies were performed. Presumably four of the infants were alive prior to delivery, but in one case the fetal heart became inaudible two hours prior to delivery. All of the umbilical plasma 17-hydroxycorticosteroid values were in the normal range, as were roughly one-half to one-fourth of the maternal values. Similar values and ratios have been reported for normal infants born by vaginal delivery. Plasma 17-ketosteroid determinations were performed in only two of the cases. In one instance, no plasma 17-ketosteroids were detected in the mother or infant, and in the other instance the levels were lower than normal.

Pathologic studies revealed that the "fetal zone" of the adrenal was missing in all five infants. In four infants no pituitary tissue could be detected with the dissecting microscope, but in one there was a "normal" pharyngeal pituitary.

Comment: Previous studies have shown that the 17-hydroxycorticosteroids found in umbilical cord plasma are largely a reflection of maternal levels and cannot be used as a basis for assessing fetal adrenal function. The normally high 17-ketosteroid values in umbilical cord plasma have previously been assumed to arise from the fetal zone of the adrenal cortex, and the low values found in the present study would tend to substantiate this hypothesis. It should be noted, however, that these data are at variance with the high 17-ketosteroid values found by Di George et al. (*J. Clin. Endocrinol.* 16:1281, 1956) in the single previously studied case. Neither of these studies shed any new light on the factors controlling the development of the fetal zone in intrauterine life.

CORRECTION

On page [6] of the index to Volume 96 (December issue), in the third listing above the center head, *Mc*, the first author's name was omitted. This listing should read:
Luhby, A. L.; Cooperman, J. M.; Teller, D. N.; Wenig, J. B., and Feldman, R.: Pattern of folic acid deficiency during folic acid antagonist therapy in children with acute leukemia and neuroblastoma, 627.

News and Comment

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in Chicago, on October 24, 25, and 26, 1958.

Adams, Erie Dell, Lubbock, Texas.
Alcorn, Robert Seba, Denver.
Bailen, J. Lewis, Bloomington, Ill.
Barron, Bernard W., Louisville.
Bean, George William, Rochester, N. Y.
Behrle, Franklin Charles, Prairie Village, Kan.
Bell, William Reed, Pensacola, Fla.
Berio, Carmen L., Santurce, P. R.
Blim, Richard Don, Kansas City, Mo.
Bock, Lewis Lincoln, Colorado Springs, Colo.
Brinkley, Joseph Wilhelm, Great Falls, Mont.
Burke-Strickland, Martha Jene, Rochester, Minn.
Burnett, Robert David, Sunnyvale, Calif.
Bush, Bartholomew M., Manhattan Beach, Calif.
Campbell, Patrick B., Elkhart, Ind.
Cassell, Norman Morton, Nashville, Tenn.
Centerwall, Willard R., Los Angeles.
Churney, Alvin M., Shively, Ky.
Cobey, William Gray, Charlotte, N. C.
Cox, Troy Vernon, Jr., Porterville, Calif.
Crawford, Kenneth P., Louisville.
Cucci, Cesare E., Jamaica, N. Y.
Cummings, John M., Jr., Leominster, Mass.
Cushing, Richard T., Minneapolis.
Dietze, Margaret R., Dearborn, Mich.
Dixon, Gloria Anne, Decatur, Ga.
Egan, Gregory J., Jr., La Crosse, Wis.
Elam, Harry P., Chicago.
Friedman, Arnold Bernard, Cleveland.
Gangeness, Leonard G., Des Moines, Iowa.
Gay, Charles Houston, Charlotte, N. C.
Gerstmann, Paul Edward, Puyallup, Wash.
Gibson, William Miles, Cleveland.
Gilmore, Robert William, Michigan City, Ind.
Glicklich, Lucille B., Milwaukee.
Goldberg, Bernard A., Studio City, Calif.
Green, L. Margaret, Atlanta.
Gyland, Stephen Paul, Jacksonville, Fla.
Hanlon, Marion L., Honolulu, Hawaii.
Hare, James Donald, Madison, Wis.
Henderson, Worth W., Royal Oak, Mich.
Hinchmann, Donovan F., Warren, Ohio.
Hummel, John H., Joliet, Ill.
Hunter, Laurel Virginia, Oklahoma City.
Ireland, William R., Covina, Calif.
Kerr, Josephine M., New York.
Knock, Henry Leroy, Jr., Clayton, Mo.
Lepow, Martha Lipson, Cleveland.
Lommel, Jerome Gregory, Detroit.
Lussky, Robert A., Wilmette, Ill.
Mack, Dorothy Louise, Shreveport, La.
Markman, Charles A., Beverly Hills, Calif.
Mason, William George, Saginaw, Mich.
Mauer, Alvin Marx, Salt Lake City.
McIllece, Patricia E., Madison, Wis.
Melgaard, Robert Thor, Dubuque, Iowa.
Mijer, Frits, Aurora, Colo.
Millikan, Martin K., Evanston, Ill.
Mitchell, Shiela Craig, Ann Arbor, Mich.
Moss, James Kingsley, Jacksonville, Fla.
Palmer, John E., Reno, Nev.
Palmgren, Carolyn Cleare, Evanston, Ill.
Papaioanou, Helen, McDowell, Ky.
Powers, Edward J., Richland, Wash.
Priest, Jean Hirsch, Seattle.
Rectanus, Daniel R., Menlo Park, Calif.
Rhodes, Jack Wylan, Charleston, S. C.
Riordan, John A., Worcester, Mass.
Rudy, Warren B., Wausau, Wis.
Rush, William E., St. Clair Shores, Mich.
Saycich, John M., Missoula, Mont.
Schaffer, Percy Samuel, Los Angeles.
Schneck, Ida Nakashima, Denver.
Schnitz, Sidney Edward, Oklahoma City.
Sigman, Cheney C., Jr., Atlanta.
Stamm, Stanley J., Seattle.
Steepe, Charles A. D., Grosse Pointe Woods, Mich.
Stewart, Sarah E., Portland, Ore.
Thiele, Ronald Lewis, Concord, Calif.
Thomas, Howard P., Jr., Telford, Pa.
Tsumori, Himeo, San Francisco.
Tytla, Elsie M., New London, Conn.
Vance, Arnold Leonard, Baltimore.
Vermillion, Margaret B., Louisville.
Walker, Gilbert Harold, Coral Gables, Fla.
Way, William Greene, Winchester, Va.
Wevers, Herman J., Fort Chaffee, Ark.
Whiteside, James A., Coral Gables, Fla.
Wilson, Ian Douglas, Detroit.
Wineberg, Julius J., Waukegan, Ill.
Woods, John Olen, Everett, Wash.
Wyngaarden, Martin K., Grand Rapids, Mich.

Special Foreign Certificates

Brillantes, Rosita Clemente, St. Louis.
Ramachandran, R. S., Madras, India.

$1,160,000 Given by Markle Fund to Support Medical Education and Talent Study.—Grants of over $1,160,000 were announced in the annual report of the John and Mary R. Markle Foundation, covering the period July 1, 1957-June 30, 1958, issued today. The largest grant announced by John M. Russell, Vice-President and Executive Director, was $750,000 appropriated to medical schools in the United States and Canada toward the support of 25 young faculty members selected by the fund as Scholars in Medical Science. The Scholar program has been the major interest of the Foundation for 11 years. During that time 231 doctors in 74 medical schools have received help from appropriations totaling $6,800,000. The Scholars chosen this year are teachers and investigators in medical schools at the following colleges and universities: Alberta, Baylor, Buffalo, California (San Francisco and Los Angeles), Colorado, Cornell, Harvard, Johns Hopkins, Kansas, Michigan, North Carolina, Northwestern, Oklahoma, Pennsylvania, Queen's, Saskatchewan, Tennessee, Vanderbilt, Medical College of Virginia, Western Ontario, Western Reserve, Wisconsin, Yale, and Yeshiva. A grant of $30,000 toward the Scholar's support was appropriated to each medical school, at $6,000 annually for five years.

The fund also appropriated $150,000 to the Association of American Medical Colleges for general development of its program and $200,000 to Washington University School of Medicine, St. Louis, to train young teachers and research workers in its basic science program.

Mr. Russell reported the findings of a study prepared by the Committee on Identification of Talent of the Social Science Research Council, under a grant of $100,000 from the Foundation. Members of the Committee were David C. McClelland, chairman, Professor of Psychology, Department of Social Relations, Harvard University; Alfred L. Baldwin, Department of Child Development and Family Relationships, Cornell University; Urie Bronfenbrenner, Department of Child Development and Family Relationships, Cornell University; Leonard S. Cottrell, Social Psychologist, Russell Sage Foundation; Fred L. Strodtbeck, Associate Professor of Social Psychology, University of Chicago, and Dael Wolfle, Executive Officer, American Association for the Advancement of Science.

The study, "Talent and Society," was undertaken "in the hope of finding out what has been done, what is being done and what should be done" to identify ability at all levels. "The free world needs to know more about how to discover those with ability and how to encourage them to make the most of it."

"While we realized that little was known about the human intangibles involved in talent, we found it frightening to have our ignorance spelled out, as it is, in this study," Mr. Russell says. For example, "A good school record does not necessarily show what a person will accomplish in later life; psychological tests of personality and ability are questioned; the factors that make up a successful career are not known; the reasons for the loss of potential talent beyond low intelligence, poor school grades or lack of money are not understood; the effect of religion, race and family background on occupational achievement and the type of work a person enters is not fully appreciated; and understanding of how talent develops, and the implications of this for education, is lacking. Many a well-nourished sacred cow looks sickly after reading this list."

"Since one of the most popular sacred cows is that good school work leads to success in later life and since good academic work is fairly easy to measure and predict, it is natural that up to now research has concentrated on making these predictions more precisely. Concentration of research on this point is one reason the Committee turned its attention to the non-academic types of talented behavior and the non-intellectual factors that affect what a man does in life. The ability a person has to understand what another is thinking, and how he will probably react, is a rough example of the former, and family background and training, as well as economic status as they affect what a person wants most from life and why he does or does not 'go places and do things,' are examples of the latter."

The Committee reported that it found the problem "even more complicated than had been anticipated. In general, it reviewed the current situation in talent research, consulted with major research groups working in the area, held meetings to clarify problems and exchange ideas, carried out research problems in needed areas, and issued the report." The report concludes, "in our rush to give every potentially talented child a break or to beat the Russians in the production of engineers, let us not forget that the quota of basic knowledge on how to solve such problems is not very large. It was the task of this Committee to try to explore ways of increasing such basic knowledge. We believe that our results justify

further efforts directed at the same objectives, and that what is needed is more long-range, venture capital to develop new theoretical resources."

The Markle Foundation was established in 1927, by the late John Markle, Pennsylvania coal operator. Grants of nearly $20,000,000 have been made during the 31 years the fund has been in existence. Since 1948, the chief interest of the Foundation has been grants for Scholars in Medical Science, all of whom are faculty members of medical schools in the United States and Canada.

ANNOUNCEMENTS

Meeting of the American Association for the History of Medicine.—The 32d Annual Meeting of the American Association for the History of Medicine will take place in Cleveland, May 21-23, 1959, at the Cleveland Medical Library. The Wade Park Manor will be the convention hotel. Chairman of Program Committee: Miss Elizabeth H. Thomson, Yale University School of Medicine, New Haven, Conn. Chairman of Local Arrangements Committee: Bruno Gebhard, M.D., Cleveland Health Museum, 8911 Euclid Ave., Cleveland.

Health Education Conference.—The 1959 Eastern States Health Education Conference of The New York Academy of Medicine will be held on Thursday and Friday, April 30 and May 1, 1959, at The New York Academy of Medicine, 2 E. 103d St., New York.

University of Wisconsin Postgraduate Program for Pediatricians.—The University of Wisconsin is presenting a postgraduate program for pediatricians April 2, 3, and 4, 1959. This two-and-one-half-day course will deal with problems of the newborn period. The guest faculty will consist of Dr. Hans Eichenwald, who will discuss the problem of infectious disease in the newborn; Dr. Clement Smith, who will discuss respiratory problems; Dr. Julius Richmond, who will discuss emotional problems; Dr. Edward Pratt, who will present nutritional and metabolic problems, and Dr. Richard Day, who will discuss the problem of icterus in the newborn period. In addition to formal lectures there will be case presentations with panel and participant discussion. At the end of each day the group will be divided into subgroups for informal seminars with one of the five members of the guest faculty. The program will be held at the new Wisconsin Post-Graduate Center Building in Madison. The course will be limited to 100 participants. The fee for the course is $35. For information or registration write to Dr. Robert Parkin, University of Wisconsin Medical School, 418 N. Randall St., Madison 6, Wis.

The National Foundation Health Scholarships.—The National Foundation, in an unprecedented effort to help overcome the critical shortages of personnel in the health field, has announced a multimillion dollar scholarship program designed to assist students of medicine, nursing, physical therapy, occupational therapy, and medical social work. This will be a first step in its new expanded program.

The *present* scholarship and fellowship program will be continued but modified and expanded where necessary. This program over the years has added over 7,600 especially trained people to those prepared to work in research and patient care.

The new Health Scholarship Program will encourage a younger age group to select a career in one of the professions at a time when they are looking to their future full of idealism and the desire to be of service in the world.

Shortages in the health field are not new to members of the health professions, but because shortages have increased the work load on each person there has been little time to take these problems to the public in an effective way.

The axiom, "only when people make some kind of financial sacrifice for their schools do they take an active and wholesome interest in education," applies not only to public but to professional schools.

Under the new program of The National Foundation, a means to create community interest in the health professions is at hand. There are 3,100 county chapters consisting of community-alert volunteers. In addition to the basic objective of adding more qualified personnel and in cooperation with the five professions concerned, three additional specific objectives are sought: (1) to stimulate interest in all of the health professions but specifically in medicine, nursing, physical therapy, occupational therapy, and medical social work; (2) to gain awareness and community understanding of the problems that contribute to the ever-increasing shortages of personnel in the health fields, and (3) to encourage cooperation and

understanding among the five professions concerned in making their professional talents available to the communities in the solution of these personnel problems.

At the press conference held to announce the new program, Basil O'Connor, President, summarized the new program as follows:

The National Foundation will offer annual Health Scholarships to help provide four years of college or university education in career preparation for five of the key professions: medicine, medical social work, nursing, physical therapy, and occupational therapy.

A minimum of 505 Health Scholarships will be offered each year, the first of them before the end of the 1959 school year. They will be made available on a geographic basis, with heavily populated states receiving as many as 25—or 5 for each of the five professions—and with no state or territory receiving fewer than 5 Health Scholarships, a minimum of 1 for each of the five professions.

The chapters of the National Foundation, numbering more than 3,100, will have an active part in the program. They will seek and accept Health Scholarship applications, pass them on to state or territorial professional committees for selection, and present awards to winners.

Health Scholarships will be made available to student citizens of the United States in each of the 49 states, the District of Columbia, Hawaii, and Puerto Rico.

Over the next 10 years this program will cost at least $12,000,000. Each scholarship awardee will receive $500 a year for four years, or a total of $2,000—providing that scholastic standards are maintained. The 505 Health Scholarships each year will cost over $1,000,000.

Because education requirements of the five professions vary, scholarships will be made available in nursing, physical therapy and occupational therapy, to all graduating high school students who have been accepted for an approved program by accredited colleges or universities; medical social work, at the college junior year, extending through two years of required graduate work, and in medicine, at the college junior, senior, or first graduate year, depending upon the requirements of the medical school.

Awards, taking financial need and scholastic achievement into consideration, will be made by state and territorial committees composed of members of the five health professions.

Renewals and payments for the second, third, and final years of the scholarships will be contingent upon satisfactory progress.

Scholarship money need not be limited to tuition but may be used to cover any appropriate student expense. Students may accept other scholarship funds, providing The National Foundation is informed of the source and amount.

Winners of scholarships are not committed to work in health fields of special interest to The National Foundation, such as polio, arthritis, or birth defects. Scholarship recipients are, however, expected to serve the health field at large, working in areas for which they are prepared.

A table of scholarships adjusted to population follows:

Population, Million	States, No.	Scholarships/State, No.	Total
Over 8	4	25	100
6-8	3	20	60
2.8-6	12	15	180
Up to 2.8	33	5	165
	52 (Includes District of Columbia, Hawaii, & Puerto Rico) Scholarships/State, No.		505

The distribution of scholarships adjusted to population is as follows:

Four states receiving 25 annual scholarships (5 in each health profession):

1. Illinois
2. Pennsylvania
3. California
4. New York

Three states receiving 20 annual scholarships (4 in each health profession):

5. Michigan
6. Texas
7. Ohio

Twelve states receiving 15 annual scholarships (3 in each health profession):

8. Kentucky
9. Minnesota
10. Alabama
11. Tennessee
12. Virginia
13. Wisconsin
14. Georgia
15. Indiana
16. Missouri
17. North Carolina
18. Massachusetts
19. New Jersey

Thirty-three states and territories receiving five annual scholarships (one in each health profession):

20. Nevada
21. Alaska
22. Wyoming
23. Delaware
24. Vermont
25. Hawaii
26. New Hampshire
27. Idaho
28. Montana
29. North Dakota
30. South Dakota
31. New Mexico
32. Utah
33. Arizona
34. Rhode Island
35. Dist. of Columbia
36. Maine
37. Colorado
38. Nebraska
39. Oregon
40. Kansas
41. Arkansas
42. West Virginia
43. Connecticut
44. South Carolina
45. Mississippi
46. Puerto Rico
47. Oklahoma
48. Maryland
49. Washington
50. Iowa
51. Louisiana
52. Florida

Postgraduate Seminar for Pediatricians.—The Eighth Annual Post-Graduate Seminar for Pediatricians will be conducted at St. Christopher's Hospital for Children, of the Pediatric Department of Temple University School of Medicine, Philadelphia, May 20-23, 1959. Half-day sessions will be devoted to various phases of pediatric medicine.

For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 3.

Books

BOOK REVIEWS

Physiology and Pathology of the Newborn. By Dr. A. F. Tur. Price, not given. Pp. 430. Government Medical Publishing House, Moscow, U. S. S. R., 1955.

This is a rather comprehensive textbook dealing with problems of the newborn, the first half of which is devoted to the physiology of the newborn and to the presentation of normal findings. Many tables set forth normal values in the premature and newborn—blood cell counts and chemistries, urinary flow and chemical content of urine, respiratory coefficient, survival of prematures related to method of feeding, body temperature, etc. A lengthy and detailed chapter is devoted to the hospital management of the full-term and premature infant.

The latter portion of the book presents the pathology of the newborn—congenital and acquired—and is discussed system by system.

There are many and satisfactory illustrations. The paper is of better than average quality for a Soviet text. The bibliography has almost one thousand references—all but fifteen of which are in the Soviet literature.

This is obviously a very valuable book for Soviet pediatricians. In the United States it would be a good reference for investigators in the area of newborn medicine, with some information and many references which may not have found their way into the English literature.

MOSES GROSSMAN, M.D.

An Introduction to Childrens' Diseases. By Dr. A. F. Tur. Price, not given. Pp. 364. Government Medical Publishing House, Moscow, U. S. S. R., 1955.

The author, Dr. A. F. Tur, is one of the leading pediatricians in the Soviet Union and the chairman of the department at Leningrad. This is a textbook of pediatrics approved for use by medical students and serving as an introduction to the clinical course in pediatrics.

After an introductory chapter on the history of Soviet pediatrics, the book deals with growth and development—physical and mental—with a fairly standard approach. About a third of the book is devoted to a systematic discussion of the anatomic and physiologic characteristics of the normal infant and child by organ system. Another third of the book is systematically devoted to methods of examination of the child and evaluation of signs, symptoms, and laboratory findings. This, too, is covered organ system by organ system.

The closing two chapters are devoted to the feeding of healthy infants and children and the fundamentals of hygiene. It is of interest that breast-feeding is felt to be far superior to bottle-feeding; solids are started at five to six months. The chapter on hygiene deals at some length with bathing, dressing, recommendation about physical education, and psychological aspects of care of the normal child. Swaddling is recommended and described in detail.

This text avoids any mention of pathology, pathogenesis, or clinical aspects of disease. It concludes with the statement that in subsequent courses the students will be introduced to diagnosis and therapy of disease states. Thus, the approach to teaching pediatrics is a full introductory course on the normal infant and child. The ideas expressed would, on the whole, be very acceptable here, except for marked differences in the cultural aspects of feeding and caring for children.

The paper and the illustrations are mediocre.

MOSES GROSSMAN, M.D.

Psychoanalytic Study of the Child. Vol. XII. Edited by R. S. Eissler et al. Price, $8.50. Pp. 417. International Universities Press, 227 W. 13th St., New York 11, 1958.

"Psychoanalytic Study of the Child," Vol. XII, like its predecessors, is a varied collection of psychoanalytic contributions of theoretical and clinical content. The nineteen papers in this volume touch on a wide range of topics with no over-all theme. Certain of the papers are noteworthy. Lustman presents a study of psychic energy and mechanisms of defense. Marianna Kris discusses the use of prediction in a longitudinal study. Erna Furman describes the treatment of children under the age of five by means of parental therapy. Elizabeth Gelleerd writes concerning psychoanalytic technique in adolescents.

ALFRED FREEDMAN, M.D.

Anomalies of Infants and Children. D. McCullagh Mayer, D.D.S., M.D., F.A.C.S., F.I.C.S., and Wilson A. Swanker, M.D., F.A.C.S., F.I.C.S. Price, not given. Pp. 454. The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1958.

Although this book was written as an aid to the general practitioner and pediatrician, in general much of the material, in my opinion, is slanted toward the nonmedical person. In places

where the subject matter is covered more thoroughly there are significant inaccuracies and omissions. As an example, in the chapters on etiology, Mongolism and sickle-cell disease are stated to be due to a dominant mutation. Although the effect of x-ray radiation on the embryo is discussed, there is no mention of associated microcephaly. Under electrolyte therapy the authors recommend a 1%-2% ammonium chloride therapy for sodium depletion in the immediate postoperative period. They also state that "little or no salt should be given a patient postoperatively for about forty-eight hours, particularly if there has been any vomiting."

After the first five chapters covering general aspects, the authors review their knowledge of malformations by region. The coverage of anomalies of the chest and abdominal cavities is purposely omitted. Each chapter is introduced by a brief discussion of the embryology of the region. The descriptive material on the face and mouth is of interest and quite detailed. Other areas are not covered in any length but often inaccurately. The newer concepts of endocrine-induced malformations of the genitalia are not mentioned.

The last two chapters are devoted to burns and accidents. There is not much of interest here, except perhaps a letter on accident prevention reproduced from the Metropolitan Life Insurance Company.

THOMAS H. SHEPARD, M.D.

Oligophrenia in Combination with Congenital Ichthyosis and Spastic Disorders. By Torsten Sjogren and Tage Larsson. Price, 25 Swedish Crowns. Pp. 112. Ejnar Munksgaards Forlag, Nørregade 6, København, 1957.

This interesting clinical syndrome has been thoroughly studied in the county of Västerbotton in the north of Sweden. The clinical picture is characterized by low-grade oligophrenia, pronounced ichthyosis, and evidence of spastic diaplegia. A detailed genealogic and geographic analysis suggested that this syndrome has its origin in a single gene mutation. This rather exhaustive study was undertaken and presented in detail in the hope that it would be of value to research workers as a study of analytic methods, pooling of case material, and a genetic analysis.

At the time of preparation of this very exhaustive and detailed genetic analysis there had not previously been described a similar clinical picture in the literature. However, within the past two years, independent case reports appearing in neurologic and pediatric journals and dealing with cases of this type have been reported both from the United States and from England.

It is felt that this very complete clinical and genetic study is of considerable interest to those in pediatrics whose interests lie in the genetic patterns of disease, especially in regard to mental deficiency.

FREDERICK A. HORNER, M.D.

No and Yes: On the Genesis of Human Communication. By René A. Spitz. Price, $4. Pp. 170. International Universities Press, Inc., 227 W. 13th St., New York 11, 1957.

"No and Yes," like preceding work of Dr. René A. Spitz, is a study of the psychological development of infants. In this work Dr. Spitz focuses upon the beginnings of verbal and somatic communication, and his purpose is to apply the psychoanalytical theory of Freud to this problem. It is Dr. Spitz's proposition that negation, as well as affirmation, arises out of inherited motor-behavior patterns which are used in the earliest nursing situation. Thus, negation, or no, arises from cephalogyric movements involved in breast-feeding. References are made to recent investigations of animal ethology, physiology, embryology, and experimental psychology in a most stimulating manner. However, in elaborating his own thesis there is a paucity of original observation. Major emphasis is placed upon the case of Monica, a girl with esophageal atresia who was fed through a gastric fistula until she was twenty-two months old, described by Engel, Reichsman, and Segal (*Psychosom. Med.* 18:374, 1956). However, this was a child who not only had a physical handicap but who also had been emotionally deprived, had a variety of difficulties in relationship to parents, and was greatly retarded (at twenty-two months, the child was given a Gesell rating of from nine to fifteen months). To draw broad conclusions concerning normal development from such a case would appear hazardous. Thus, while "No and Yes" is a most provocative and interesting book the hypotheses presented would appear to require further validation.

ALFRED FREEDMAN, M.D.

Heredo-Retinopathia Congenitalis Monohybrida Recessiva Autosomalis: A Genetical-Statistical Study. By Carl H. Alström. (Laboratory for Human Genetics, Psychiatric Clinic of Caroline Institute, Stockholm, Sweden) and Olof Olson (State Institute for the Blind, Tomteboda, Stockholm, Sweden). Price, not given. Pp. 178, with 30 tables and 9 illustrations. Berlingska Boktryckeriet, Lund, Sweden, 1957.

This is a monumental study of 175 cases of a hereditary form of congenital blindness or severe impairment of vision, with 303 unaffected siblings in the 105 families concerned. A brief account is given of an extensive genealogic investigation in which more than eight thousand ancestors were traced. It was found that twenty-nine of the one hundred five families belong to five large family complexes.

The mode of inheritance of the disease was found to be monohybrid, recessive autosomal, with complete penetrance. The disease is responsible for about ten per cent of the cases of blindness in children who reach school age in Sweden, with a frequency in the general population of about three in one hundred thousand and a heterozygote frequency of between one-half and one per cent.

Vision is defective at birth, with either total blindness or greatly impaired sight with loss of central vision. There is general deterioration of the remaining vision.

Youthful patients had either normal fundi or exhibited sparse round pale spots or round or irregular pigmented dots in the peripheries. Macular changes were seldom seen. These changes and the pigment clumping progressed slowly with age. Only after the age of fifty could widespread chorioretinal atrophy be seen. Pallor of the disks and narrowing of the vessels progressed with age. An extinguished electroretinogram was found in ninety-two per cent of the sixty-two patients on whom this examination was done, and flicker electroretinography was abnormal in the other eight per cent. This confirms the inference that the hypothetical biochemical process which underlies the disease involves primarily the retinal elements.

An almost constant feature was nystagmus of the irregular searching type. Cataract and keratoconus were common features and increased in frequency and severity with age. There were no accompanying psychiatric or neurologic disorders. There was no increased frequency of deafness in the family trees of the affected patients, and no classic case of retinitis pigmentosa was recorded.

A pathologic examination has not so far been obtained.

ROBERT W. HOLLENHORST

Modern Problems in Pediatrics. Edited by A. Hottinger, F. Hauser, and H. Berger. Price, Swiss Fr. 96. Pp. 592, with 129 illustrations. S. Karger AG., Arnold Böcklinstrasse 25, Basel, 1958.

This collection of review articles represents a laudable effort on the part of its judicious editors, Hottinger, Hauser, and Berger. They obtained the cooperation of authors prominent in their respective fields to present short, concise, informative papers.

These contributions are concerned with immunohematology and inborn errors of metabolism. Each paper is followed by a wealth of pertinent bibliography. Most articles are of superior quality. Impressive are the paper by Dausset on the immunohematology of leukocytes, Berger's thorough discussion of chronic amino-acidurias, and Schreier's review of the inborn errors of phenylalanine metabolism. Cori summarizes the clinical and biochemical differences in four types of glycogen-deposition disease; Holzer, the present status of galactosemia. Zöllner appears to follow very closely in the steps of his former teacher, Thannhauser, in reviewing disorders of fat metabolism and is at least equally thorough.

Of great interest are the articles by Bickel on Wilson's disease, Burke on oxalosis, Zetterström on idiopathic hypercalcemia, and Lowe and Bruce on organic amino-aciduria. The authors discourage the use of microbioassays for the determination of individual amino acids in serum and urine. This seems unjust, since very accurate data have been obtained by the use of this method—more accurate, in fact, than those obtained by paper chromatography.

Swoboda reviews the problem of hypophosphatasia. Although he mentions that there are approximately twenty cases known, by now the figure seems to be closer to forty. The author's observation of low magnesium values may be of importance.

The only disappointing paper was Vorlaender's discussion of the immunology of rheumatic fever and glomerulonephritis. A considerable amount of speculation is presented in lieu of definite facts.

It is my opinion that this book should be a part of the libraries of pediatric centers and of physicians interested in immunohematology and problems of inborn errors of metabolism. Sixteen of the papers are written in German and five each in French and English.

GUNNAR B. STRICKLER, M. D.

Infectious Diseases of Children. By Saul Krugman, M.D., and Robert Ward, M.D. Price, $10. Pp. 340, with 44 illustrations and 7 color plates. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1958.

This modest-sized and relatively inexpensive book might well bear the longer title "Common Infectious Diseases of Children in U. S. A.," since the rare and unusual have been omitted. For instance, syphilis, malaria, and rabies are not covered, but there are excellent chapters on adenovirus and staphylococcal infections and aseptic meningitis. The strong points of the book are the thoroughly authoritative and up-to-date treatment of the common childhood diseases and its conciseness and brevity. In the section dealing with infections, in which knowledge is being accumulated rapidly, there is much material only a few months old. The authors have discarded many myths regarding infectious diseases and have substituted documented evidence, and they avoid being dogmatic over controversial points. The charts, diagrams, and photographs (seven in color) are excellent. Discussions of treatment are in general terms. An interesting section on the hospital care of patients with infectious diseases reflects a far more relaxed attitude regarding isolation procedures than formerly generally held.

The book is clearly designed for those learning infectious diseases for the first time and for those who may have need for a reference to important specific facts concerning them. For the pediatrician requiring more detailed discussion an excellent bibliography accompanies each chapter.

WARREN E. WHEELER, M.D.

Poisoning: A Guide to Clinical Diagnosis and Treatment. Second edition. By W. F. Von Oettingen, M.D., Ph.D. Price, $12.50. Pp. 650. The W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

The second edition of this standard work on poisoning will be of greatest usefulness to the industrial physician called on to treat acute poisoning with known modern chemicals. A rather encyclopedic discussion of the various poisons which may cause individual symptoms would appear to be of doubtful usefulness except in the rare instance of poisonings due to unknown substances. The section on qualitative confirmatory laboratory tests for many items appears to be excellent.

The book is clearly not designed for and will not be of much help in the treatment of accidental poisonings in childhood, where the vast majority of such poisonings occur. There is no attempt made to indicate the poisonous contents of common household articles or even of classes of household articles. The brief description of symptoms and treatment of poisoning due to individual substances is weakened by the general failure to indicate lethal doses or order of toxicity. As far as it goes, the discussions should be considered authoritative.

WARREN E. WHEELER, M.D.

Pediatric Surgery. By Orvar Swenson. Price, not given. Pp. 730, with 448 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1958.

This is a practical book designed to acquaint the young medical school graduate with the accepted techniques of practical treatment of pediatric surgical problems. Its greatest value is in giving detailed descriptions of simple procedures used in the care of the pediatric surgical patient. Of particular value and charm are the early chapters describing some of the tricks learned from long experience of how to woo the faith and respect of the child being prepared for surgery and anesthesia.

The book is profusely and often needlessly illustrated. There are, for example, the inevitable before-and-after surgical pictures of perfectly normal looking youngsters in almost every chapter that seem to plague pediatric and plastic surgeons in this era. In many chapters these half- and full-page pictures occupy space that might have been used for a more exhaustive discussion of the surgical problem involved.

The author's surgical interests are reflected in the inordinate amount of space given some lesions and the relative neglect of others. For example, a total of ninety-two pages (or

thirteen per cent of the entire book) is devoted to Hirschsprung's disease and megaloureter. Postoperative fluid care is covered in five pages, two of which are taken by surface area nomograms!

This, then, is alternately—and somewhat unevenly—a combination of a pediatric surgical textbook, surgical atlas, and pediatric manual with no pretense to being exhaustive in any of these categories. It will be of most value as a reference book for the young pediatrician who wants a general knowledge of pediatric surgical problems.

HENRY C. KEMPE

The Normal Child. By Ronald S. Illingworth, M.D., F.R.C.P., D.P.H., D.C.H. Price, $7. Pp. 356. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

This book, according to the author, is designed for physicians. In its preface he states that it sets out to give the doctor as much help as possible in trying to decide whether an individual child is normal or abnormal and to give him as much guidance as possible in the management of simple behavior problems. "It is intended for all doctors who are concerned with the care of children, especially family doctors and doctors in the Child Welfare Service."

The book contains a section on feeding problems, under which are included "Breast-Feeding or Artificial Feeding, The Feeding Schedule, Some Breast-Feeding Problems, Breast and Nipple Difficulties, Insufficiency of Milk, Difficulties in the Breast-Fed Baby and in the Artificially Fed Baby." Another section deals with physical problems and includes various physical assessment methods, such as height and weight, and, curiously, the prevention of infection. Section 3 deals with developmental problems, including mental development and developmental diagnosis. Section 4 is labeled "Behavior Problems" and includes instructions on discipline and punishment, proper parental attitudes and their management, sleep problems, jealousy, the prevention of accidents, and the proper toys to select. The author's specificity of instruction is well illustrated by his recommendations of what to do when the child refuses to lie down when put to bed. He states that he should be left sitting or standing up. The author confesses he does not have any answer to the problem of the child who wakes up at 5 a. m.

This volume is curious in the diverse nature of the material presented. It stresses the importance of individual differences, and parts of it are strongly Gesellian in orientation, yet it devotes as much as three-fourths of a page, including photograph, to such a topic as the easiest and quickest way to feed twins on the breast. The easiest and quickest way, as one might surmise, is to feed the two simultaneously, one on each breast. The author does not offer any solution to the problem of feeding triplets in a hurry.

In instructing on the interpretation of measurements in physical growth, physicians are warned that errors in measurement often occur from scales which are out of order and that differences in weight may occur because the child is weighed with clothes on in one instance and naked in another or before or after feeding, in the case of very young infants. Caput succedaneum is explained, as are the fontanelles, cephalhematoma, craniotabes, etc. Five lines are devoted to the topic of undescended testes; pulse rates a paragraph of three lines; the prediction of personality is dealt with in slightly more than two pages.

The book is very readable, and there are spots of information which I am sure would be usable to many physicians. It is a little hard to conceive, however, how such sections as that on "Care of the Breast, Infant Feeding," etc. could possibly be omitted in the course of normal medical school training in any Grade-A medical school. If any of our current graduates are being turned out with less information on such subjects than is contained in this volume, then we have cause for grave alarm.

It is my feeling that the author would have been better advised to assume a greater sophistication on the part of his reading public and omit many of the subjects he covers. He would then be able to develop those with which the average medical man is poorly informed to a much more adequate degree.

LESTER W. SONTAG, M.D.

The Management of Childhood Asthma. By Frederic Speer, M.D. Price, $4.75. Pp. 116, with 8 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

The author has attempted to simplify the management of a condition which often needs more careful study than it sometimes receives.

The asthmatic child and his family are discussed as a unit, and the importance of parental understanding and cooperation is stressed. The associated problems of childhood asthma are

described, and the various important etiological factors are outlined. The step-by-step approach in making a specific etiological diagnosis is detailed in the discussion of hypothetical cases.

Treatment of the asthmatic attack is discussed in the light of most modern methods, and prophylactic and hyposensitization measures are outlined for the reader.

This small book is recommended to all physicians who treat children.

LEWIS A. KOCH, M.D.

Einführung in die Kinderheilkunde. Fourth edition. By E. Glanzmann. Price, $17.85. Pp. 1068, with 301 illustrations. Springer-Verlag, Mölkerbastei 5, Wien I, 1958.

This is the fourth edition of "Einführung in die Kinderheilkunde" (Introduction to Childhood diseases), by E. Glanzmann.

The content of the book consists of a total of two hundred seven lectures, divided into twenty-three sections.

The first five lectures deal with the duties and goals of pediatrics, growth and growth factors, and water and caloric requirements of infants. In the following fifteen lectures, mainly nutritional requirements and vitamins are discussed.

The third, fourth, and fifth chapters, consisting of thirty-nine lectures, are devoted to the various types of feedings and nutritional disturbances in the period of infancy.

In the seventh chapter, the author discusses the two commonest problems in pediatrics, enlarged abdomen and recurrent abdominal pains in children. Diseases of intestines, liver, spleen, and pancreas are also included.

In the eighth chapter, under the heading of "Diseases of the Blood," erythroblastosis fetalis, techniques and indications for exchange transfusions, nutritional anemias, congenital hemolytic erythropathias, acute leukemias, coagulation abnormalities, heredofamilial defects of the platelets, bleedings in newborn period, and infectious reticuloendotheliosis are well discussed in twenty-four individual lectures.

Chapter 9 contains thirteen lectures concerning comprehensive reviews of genetics and disorders of the endocrine organs.

In Chapter 10, the syndromes with multiple congenital abnormalities, such as Bonnevie-Ullrich, Lawrence-Moon-Bardet-Biedl, and familial dysostosis cleidocranialis, are described and illustrated.

Renal diseases and diseases of the heart, the bronchial tree, and the lungs are discussed in twenty subsequent lectures in the eleventh, thirteenth, and fourteenth chapters.

Chapters 15 and 16 are mostly concerned with infectious diseases. Diseases caused particularly by cocci are explained in great detail.

The chapter on modern chemotherapy and antibiotics gives a full account of their natural history, indications, and use.

The last six chapters include viral diseases, nonbacterial diseases of the central nervous system, chronic infectious diseases (tuberculosis, rheumatic fever, and syphilis), worm infestations, diseases of muscles in childhood, and, lastly, neuroses in children. They are discussed in forty-one comprehensive lectures.

The author does not include references, but the content of the book is undoubtedly up to date with recent advances in pediatric medicine. The text is lucid and makes very pleasant reading, and the illustrations, which are self-explanatory, give additional value to its content. "Einführung in die Kinderheilkunde" is highly recommended to practitioners, to medical students, and to any physician who has a special interest in pediatrics.

A. M. YUCEOGLU, M.D.

A Primer of Cerebral Palsy. By Joseph D. Russ, M.B., M.D., F.A.A.P., F.A.A.C.P., and Hyman R. Soboloff, B.A., M.B., M.D., F.A.A.O.S., F.A.A.C.P. Edited by John A. Anderson, M.D. Price, $4. Pp. 69, with 16 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

The authors have developed in sixty-nine pages a surprisingly complete description of the diagnosis, classification, and treatment of cerebral palsy. The value of total evaluation of the patient is stressed, and proper emphasis is given to the emotional needs and associated handicaps these patients invariably have. The book summarizes and reflects the thinking of other noted authorities in the field of cerebral palsy. The material should be valuable to medical practitioners as well as to those professional workers in the various ancillary services who render treatment to the cerebral palsied child.

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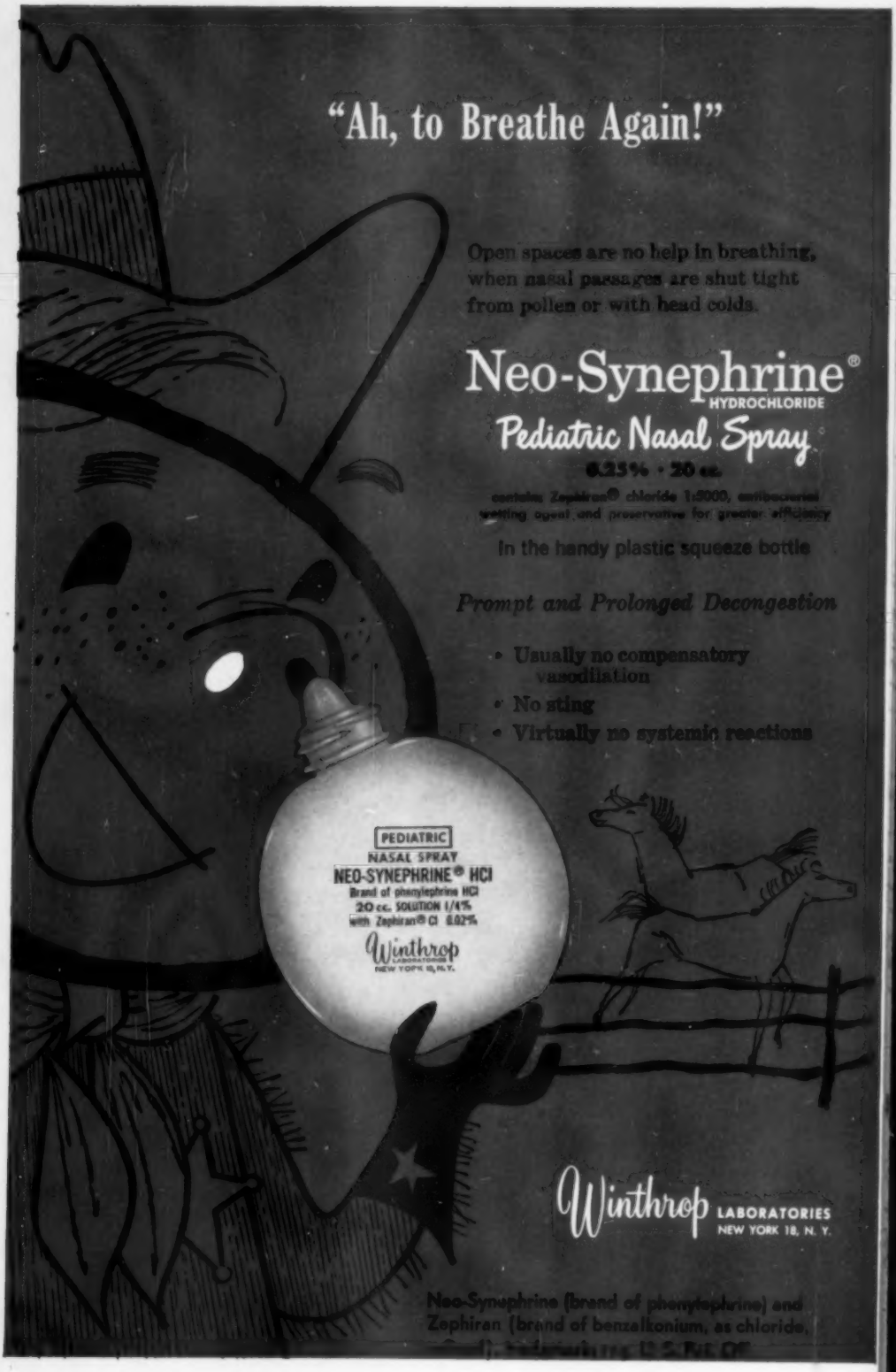
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